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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7J
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Title Page

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Volume 1 of 2
Draft Report for Task Order No. UIC-7J

FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR242511

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

June 3, 1994

Performing Laboratory

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This study evaluated the toxicity of WR242511 tartrate in dogs following four weeks of daily administration by gelatin capsule. Dose levels studied were 0, 0.1, 0.3 and 1.0 mg base/kg/day. The primary toxic effects of WR242511 were seen in the RBCs, lungs and platelets. Although subtle, hemolytic anemia was supported by reticulocytosis, secondary splenic extramedullary hematopoiesis and bone marrow hyperplasia in high dose animals. A slight, statistically insignificant decrease in body weight (-0.6 kg) was also seen in high dose males and females. Methemoglobinemia, the desired pharmacologic effect, accompanied by clinical signs of cyanosis (blue gums, tongue and sclera), and mild to moderate thrombocytopenia were observed in mid and high dose animals. WR242511 treatment induced interstitial pulmonary inflammation in seven out of eight high dose animals. Minimal, but significant increases in serum AST, globulin, and triglyceride levels in high dose males and decreases in albumin levels and A/G ratio in both high dose males and females, not accompanied by corresponding histopathologic changes in the liver, suggests that WR242511 is marginally hepatotoxic. Additionally, increased serum haptoglobin levels, indicative of an acute phase reaction, were observed in mid dose males and high dose animals. Because the aforementioned toxic responses were limited to the mid and high dose levels, the no-observed effect level (NOEL) of WR242511 tartrate was 0.1 mg base/kg/day.

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STATEMENT OF COMPLIANCE

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To the best of my knowledge, Study No. 134 entitled "Four Week Oral Toxicity Study of WR242511 in Dogs" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS
STUDY NUMBER: 134

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 11/19/93

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 11/22/93, TO STUDY DIR 11/22/93, TO MGMT 11/22/93
PHASES: PROTOCOL REVIEW

INSPECT ON 4/14/94, TO STUDY DIR 4/15/94, TO MGMT 4/18/94
PHASES: ANIMAL RECEIPT, BODY WEIGHT, AND QUARANTINE

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PHASES: CLINICAL OBSERVATION AND BODY WEIGHT

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PHASES: DOSING AND CLINICAL SIGNS

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FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS

DRAFT

Test Article: WR242511 Tartrate

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5014

Sponsor Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

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Clyde W. Wheeler, Ph.D. Date
Senior Toxicologist

Study Initiation: November 19, 1993
Dosing Initiation: May 5, 1994
In-Life Completion: June 3, 1994

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1. SUMMARY

This study evaluated the toxicity of WR242511 tartrate in dogs following four weeks of daily administration by gelatin capsule. Dose levels studied were 0, 0.1, 0.3 and 1.0 mg base/kg/day. The results are summarized in Table 1. The primary toxic effects of WR242511 were seen in the RBCs, lungs and platelets. Although subtle, hemolytic anemia was supported by reticulocytosis, secondary splenic extramedullary hematopoiesis and bone marrow hyperplasia in high dose animals. A slight, statistically insignificant decrease in body weight (-0.6 kg) was also seen in high dose males and females. Methemoglobinemia, the desired pharmacologic effect, accompanied by clinical signs of cyanosis (blue gums, tongue and sclera), and mild to moderate thrombocytopenia were observed in mid and high dose animals. WR242511 treatment induced interstitial pulmonary inflammation in seven out of eight high dose animals. Minimal, but significant increases in serum AST, globulin, and triglyceride levels in high dose males and decreases in albumin levels and A/G ratio in both high dose males and females, not accompanied by corresponding histopathologic changes in the liver, suggests that WR242511 is marginally hepatotoxic. Additionally, increased serum haptoglobin levels, indicative of an acute phase reaction, were observed in mid dose males and high dose animals. Because the aforementioned toxic responses were limited to the mid and high dose levels, the no-observed effect level (NOEL) of WR242511 tartrate was 0.1 mg base/kg/day.

2. INTRODUCTION

This study was conducted to assess the specific target organ toxicity, dose-response relationships and a potential no-observed effect level (NOEL) of WR242511 tartrate in dogs following four weeks of daily oral (gelatin capsule) administration. The study was conducted in accordance with the specifications of the Sponsor, as indicated in Task Order UIC-7J. The FDA requires the use of two animal species, one which is a non-rodent, in preclinical toxicology studies. The Beagle dog used in the study is a standard and accepted non-rodent species for regulatory toxicology studies, and was specified by the Sponsor. Oral administration is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc. designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on May 5, 1994 and the in-life portion was terminated on June 3, 1994.

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 Tartrate (Bottle No. BM05816, Lot No. DJD-08-235), a fine yellow powder, was received on December 15, 1992 and June 16, 1992 from Herner & Co., and was assigned an in-house chemical number (1720614). The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL Tartrate and the mole fraction of the base is 0.71. It was stored at -15 to -20°C and ambient humidity, and protected from light in an amber bottle.

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined to be 99.51% ± 0.02%. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was 99.50% ± 0.03%. Thus, the test article was stable under storage conditions.

3.2 Animals

A shipment of male and female Beagle dogs was obtained from Marshall Farms, North Rose, NY on April 14, 1994. The animals were approximately 6 - 7 months old (birth dates between September 15, 1993 and September 30, 1993) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a facility-unique animal number upon arrival. This number immediately appeared as a tag on a chain collar, and was additionally tattooed in the inner aspect of the ear on the same day. Animals were singly housed in runs, except as subsequently noted, in a temperature (72 ± 6°F) and humidity (50 ± 20%) controlled room with a 14 hour light/10 hour dark cycle. During the quarantine/pretest period, the animals were occasionally housed two/run within sex. The run size, typically at least 15 square feet, was adequate to house dogs at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All runs were cleaned and fresh bedding was replaced daily. The runs were sanitized once every two weeks.

Certified Canine Diet No. 5007 (PMI Feeds Inc., St. Louis, MO), approximately 400 g, was provided daily from arrival until termination. Exactly 400 g were provided when food consumption was measured. The food was removed for an overnight fast (≈ 16 - 20 hours) prior to blood collection and scheduled sacrifice. Tap water was provided *ad libitum* from an automatic watering system in which the room distribution lines were flushed daily from arrival until termination. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

Animals were quarantined for approximately three weeks. Body weights and physical examinations were done upon the dogs' arrival at the animal facility. Additionally, each dog was lightly sprayed upon arrival with Para Pyrethrin Mist for fleas, lice, and ticks. Blood samples were collected within one week of arrival for quarantine clinical chemistry and hematology tests, and fecal samples were collected for internal parasites examinations. All dogs had been previously vaccinated against canine distemper, infectious canine hepatitis, leptospirosis, parainfluenza, parvo, oral papilloma, and rabies by the animal supplier. For approximately three weeks prior to dosing initiation, the animals were observed daily for signs of illness and all unusual observations were reported to the Study Director, Toxicologist, or Clinical Veterinarian. Animals were examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test.

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3.3 Experimental Design

Near the end of the quarantine/pretest period, 16 animals of each sex were selected for study on the basis of quarantine data including body weight, food consumption, clinical pathology, electrocardiograms, and ophthalmology examinations. These animals were randomized within sex into the groups shown in the following table using a restricted randomized procedure stratified by body weight. No litter mates were included in the same dose group. Following allocation to treatment groups, the animals were randomly assigned to one of three animal rooms used for this study.

Treatment Group	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	0	4	4
2	0.1	4	4
3	0.3	4	4
4	1.0	4	4

WR242511 dose levels were selected on the basis of a previously conducted four week oral dose range-finding study in dogs (UIC/TRL Study No. 133). The number of animals, 4/sex/dose, is routinely used in regulatory studies, and also is the number of animals for this species indicated in the FDA 1992 draft document entitled "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Redbook II), Short-Term Toxicity Tests with Rodents and Non-Rodents". No such FDA document exists for the testing of drugs.

Following treatment group allocation, the animal's number appeared on a card visible on the front of each run. The run card additionally contained the study number, test article identification, treatment group number, sex and dose level. Run cards were color-coded as a function of treatment group.

The test article was administered once daily by gelatin capsule starting with day 0 (May 5, 1994) for four weeks. All animals received empty gelatin capsules (size 000, capacity 1.37 ml) for the last 3 days during week -1 to acclimate them to the procedure. The quantity of the test article (mg/kg/day) was adjusted based on the animal's most recent body weight. Control animals received empty gelatin capsules. The animals were dosed up to and including the day prior to scheduled necropsy on days 28 or 29. The dogs weighed 9.1 - 10.9 kg (males) and 7.9 - 9.9 kg (females) and were approximately 7 - 8 months old on day -3 (most recent body weight prior to initiation of treatment).

Non-fasted body weights were recorded on day -10 (randomization) and day -3, and weekly thereafter. Fasted weights were collected at scheduled termination. Clinical

signs were observed and recorded once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and coat were observed for all animals. The animals were also observed immediately prior to dosing and in the afternoon for moribundity/mortality. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in week -1, on day 0 prior to dosing, and once weekly thereafter. Food consumption was measured for all animals over an approximate 24 hour period twice in the pretest period and once weekly commencing on day 5.

Hematology and clinical chemistry parameters were measured following an overnight fast in week -1/-2, in week 2 (day 14) and in week 5 (days 28/29) at termination. In addition, overnight fasted methemoglobin levels were measured weekly just prior to dosing, commencing on day 0. The animals were unanesthetized and sufficient blood was collected from the jugular vein to measure the following parameters in random order. Water was available *ad libitum* during all fasting periods. Clinical pathology methodology is contained in Appendix 2.

Hematology

Activated partial thromboplastin time
Erythrocyte count
Erythrocyte morphology
Heinz bodies
Hematocrit
Hemoglobin
Leukocyte count, total and differential
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
[a]Methemoglobin
Platelet count
Prothrombin time
Reticulocyte count

[a]Measured with a Co-oximeter (Instrumentation Laboratory, Model No. 282). The assay was performed within one-hour of sample collection. The specimens were kept on wet ice prior to analysis.

Clinical Chemistry

Alanine aminotransferase (ALT)
Albumin
Albumin/globulin ratio (calculated)
Alkaline phosphatase
Aspartate aminotransferase (AST)
Calcium
Chloride
Cholesterol
Creatinine
Creatine kinase (CK)
Gamma glutamyl transferase
Globulin (calculated)
Glucose
Haptoglobin
Lactate dehydrogenase (LDH)
Phosphorus (inorganic)
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Urea nitrogen (BUN)

Urine specimens were collected following an overnight fast at scheduled termination in week 5. The following parameters were measured.

Urinalysis

Qualitative
- Bilirubin
- Glucose
- Ketones
- Occult Blood
- Leukocytes
- Nitrite
- pH
- Protein
- Urobilinogen

Color
Specific Gravity
Microscopic examination of spun sediment

Additionally, ≈ 2.5 ml of blood was collected from the jugular vein weekly, just prior to dosing, beginning on day 0 for the separation and isolation of plasma and cellular blood components according to the Sponsor's directives. The plasma and cell fractions resulting from separation by centrifugation were sent to COL Thomas Brewer, WRAIR, as specified by the Sponsor. The results obtained from these samples are not included in the study report.

ECG tracings were collected from all dogs during the pretest period and in week 4. The following leads were measured: I and aV_F. Heart rate, duration of the P wave and PR, QRS and QT intervals were measured from Lead I. All recordings had a sensitivity of 1 mV/cm and a recording rate of 50 mm/sec. The recordings were collected with the animal in the standard position of right lateral recumbency. In order to obtain all of the ECG's within a few days at each time point, the recordings were collected throughout the day during the pretest period, but were performed in week 4 in the afternoon, at least 2 hours after dosing.

All animals survived the four week treatment period and were sacrificed and necropsied in random order over two consecutive days (days 28/29). This was accomplished by sodium pentobarbital anesthesia (i.v.; 20-30 mg/kg) and exsanguination. An extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass to include the external surface, all orifices, the cranial cavity, external surface of the brain, cross section of the spinal cord, the nasal cavity and nasal turbinates, thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs. The following tissues and organs were collected and fixed in 10% neutral buffered formalin (NBF).

used for pair-wise comparisons with the concurrent control group . Food consumption data were analyzed by the Kruskal-Wallis test. If a significant effect was obtained ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons with the concurrent control group. All statistical analyses procedures compared treated to control animals at each time point. Data were not corrected for baseline values, except that body weight gain analysis included weekly changes and total weight changes. In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form.

4. RESULTS

4.1 Mortality/Clinical Signs

The summary of clinical signs are presented in Table 2. Individual clinical signs and daily incidence of clinical signs are contained in Appendix 3.

No animals died during the study. Treatment-related daily clinical signs of cyanosis (1 - 2 hours post-dosing) were limited to the two highest dose levels. Biologically significant signs of cyanosis were generally not observed in the low dose level, although mild (easily seen blue color) blue tongue and mild blue sclera was observed on separate occasions in two low dose females. Mild blue tongue, sclera and/or gums were observed in all mid dose animals. Marked (deep blue-purple color) blue tongue and/or gums was observed occasionally in two mid dose males and in all mid dose females. Mild blue sclera and mild to marked blue gums and/or tongue were observed in all high dose animals during the study. Marked blue sclera was observed once in one mid dose female and on several occasions in one high dose female. Marked blue gums and tongue were seen to a greater extent in high dose animals than in mid dose animals.

4.2 Body Weight

The summaries of body weights are presented in Tables 3.1 and 3.2. The summary of body weight gains are shown in Tables 4.1 and 4.2. Summaries of male and female body weights are also graphically depicted in Figures 1 and 2, respectively. Individual body weights and individual weight gains are contained in Appendix 4.

Although not significant, a decrease in body weight (-0.6 kg) was observed in high dose males and females. All other groups including control animals demonstrated a slight increase in total body weight gain (0.1 - 0.4 kg) during the treatment period.

4.3 Food Consumption

The summaries of daily food consumption are presented in Tables 5.1 and 5.2. Individual food consumption data are shown in Appendix 5.

Food consumption was not affected by treatment.

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4.4 Clinical Pathology

Summaries of clinical chemistry tests are presented in Tables 6.1 - 6.44. Individual clinical chemistry data are shown in Appendix 6. Summaries of hematology tests are presented in Tables 7.1 - 7.42. Individual hematology data are shown in Appendix 7. Summaries of urinalysis tests are presented in Tables 8.1 - 8.4. Individual urinalysis data are shown in Appendix 8.

Clinical chemistry parameters were unaffected on day 14. In week 5 (days 28/29), slight, but significant increases in serum AST, globulin and triglyceride levels (Tables 6.3, 6.9 and 6.21) and decreases in albumin levels with a corresponding reduction in the albumin/globulin (A/G) ratio (Tables 6.7 and 6.11) were seen in high dose males. At that time, a slight decrease in albumin (Table 6.8) was observed in high dose females resulting in a decrease in the A/G ratio (Table 6.12). Total serum protein levels were unaffected in either sex (Tables 6.5 - 6.6). On several occasions, the serum haptoglobin levels (Tables 6.43 and 6.44) were below the detection limit (< 13 mg/dl). At termination (days 28/29), a large increase in serum haptoglobin levels was seen in high dose animals and mid dose males. All mid dose female haptoglobin values were < 13 mg/dl. The occurrence of increased levels of this protein, which is synthesized by hepatocytes, is indicative of an inflammatory response, i.e. an acute phase reaction.

In Week 5, a slight, statistically significant decrease in MCHC was seen in high dose males (Table 7.11). A similar decrease, which failed to make statistical significance, was seen in high dose females (Table 7.12). Although RBCs were hypochromic in high dose animals, the marginal decreases in RBC count, hematocrit and hemoglobin concentration in these animals were not statistically significant (Tables 7.1 - 7.6). As a result of the minimal anemic state, compensatory increases in reticulocyte counts were seen in high dose animals (Tables 7.13 and 7.14). Although not statistically significant, elevated numbers of nucleated red blood cells in high dose females were also apparent (Table 7.16). In addition, compensatory increases in MCV (macrocytosis) were seen in high dose animals and in mid dose females, but again these mild changes failed to achieve statistical significance (Tables 7.7 and 7.8). Polychromasia (typically due to increased numbers of degenerating RBCs) and anisocytosis (irregularities in RBC size) may have occurred to a slightly greater extent in mid and high dose animals, compared to control and lower dose animals (Appendix 7). None of the above drug effects were seen after two weeks of treatment.

Methemoglobinemia was observed in mid and high dose animals throughout the study [week 2 (first time point tested after initiation of dosing) through week 5 (termination)]. Mean methemoglobin levels ranged from 6.2 - 8.6% and 7.4 - 10.0% in mid dose males and females, respectively and 24.7 - 27.2% and 23.5 - 29.4% in high dose males and females, respectively (Tables 7.19 and 7.20). Peak methemoglobin levels were observed after two weeks of treatment (week 3). An approximate two-fold increase in methemoglobin levels, although not statistically significant, was generally seen in low dose animals compared to respective controls.

Significant thrombocytopenia was observed in mid dose (week 5) and in high dose [weeks 2 (males) and 5] animals (Tables 7.37 and 7.38). In week 5, decreases in platelet count ranged from 55% - 65% in high and mid dose animals as compared to respective controls within sex. This was supported by hematology morphology observations, which demonstrated marked to moderate decrease in platelet number in mid and high dose animals (Appendix 7). Platelet clumping was also observed in the blood smears in these groups.

Urinalysis parameters were not affected by WR242511 treatment.

No other changes in clinical pathology parameters were considered to be related to WR242511 treatment. Sporadic increases and decreases were seen, but were not considered to be biologically significant. The reductions in urinary pH in mid and high dose males at termination were slight and not considered to be biologically significant.

4.5 Electrocardiographic Examinations

The Cardiology Report is contained in Appendix 9.

There were no significant ECG changes produced by WR242511 treatment. Any changes observed were considered incidental findings and not test article-related. In week 4, the elongated PR interval observed in mid dose females was considered spurious and not biologically important as these changes were not seen in high dose animals.

4.6 Ophthalmology Examinations

The Ophthalmology Report is contained in Appendix 10.

No treatment-related ophthalmic changes were observed.

4.7 Organ Weights

Organ weight summaries for % brain weight are in Tables 9.1 and 9.2. Individual organ weight data are contained in Appendix 11.

Splenomegaly was seen in high dose animals (Tables 9.1 and 9.2). Mean splenic weights were increased approximately 80% and 150% in high dose males and females, respectively, compared to controls. This was not seen in lower dose animals, and no other organ weights were affected by drug treatment.

4.8 Pathology

The Pathology Report is contained in Appendix 12. A summary of gross and microscopic lesions is shown in Table 10.

The oral administration of WR242511 was associated with microscopic changes in lung, spleen and bone marrow. Minimal to mild interstitial pulmonary inflammation was observed in high dose animals. This change was characterized by patchy to confluent infiltrates of mixed inflammatory cells (including macrophages, neutrophils and lymphocytes) within the alveolar lumina, septae and along the adventitial connective tissue of pulmonary blood vessels. The gross observation of white or yellow foci on the apical lobes of the lungs in three high dose animals (animal nos. 8144, 8182 and 8196) correlated with the presence of interstitial inflammation.

Minimal to mild splenic extramedullary hematopoiesis (EMH) consisting of clusters of erythropoietic cells along with occasional megakaryocytes was seen in all high dose animals. Although one low dose male also had minimal EMH, this was not considered to be a test article-related change because corresponding changes were not seen in mid dose animals.

Minimal to mild hyperplasia of the bone marrow was seen in all high dose animals. This change was characterized by a diffuse increase in cells regarded as myeloid and erythroid precursors replacing normal fat deposits in most of the marrow compartment. In some animals, erythroid cells appeared to be slightly more abundant than myeloid elements.

No other microscopic changes were considered to be related to WR242511 treatment.

5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of WR242511 tartrate in dogs following four weeks of daily administration by gelatin capsule. The dose levels were 0, 0.1, 0.3, and 1.0 mg base/kg/day. The results of this study are summarized in Table 1. No animals died during the study. Biologically significant clinical signs of cyanosis, characterized by blue gums, sclera and tongue, were seen in mid and high dose animals. Marked blue tongue and gums (deep blue-purple color) were observed to a greater extent in high dose animals than in mid dose animals. Clinical signs of cyanosis were not seen in the low dose animals, except for two sporadic observations. A slight decrease in body weight (-0.6 kg), not accompanied by a significant decrease in food consumption, was seen in the high dose groups. This was not seen in the lower dose levels. No treatment-related ophthalmic or ECG changes were observed during the study.

Minimal treatment-related anemia, consisting of slight, but statistically insignificant decreases in RBC count, hemoglobin and hematocrit, were seen in high dose animals. Compensatory responses to the anemia included reticulocytosis and possible macrocytosis and increased

numbers of nucleated RBCs in high dose animals. The anemia was also accompanied by secondary histologic changes including splenic extramedullary hematopoiesis (supported by splenomegaly) and bone marrow hyperplasia in high dose animals. This latter lesion suggests hemolysis as the mechanism of anemia, although hemosiderosis was not seen microscopically in the spleen, liver or bone marrow. Methemoglobinemia, the desired pharmacologic effect, was observed at the two highest dose levels throughout the study. The methemoglobin levels were maintained at a relatively constant level during the course of the study. The production of methemoglobin indicates an oxidant nature of the drug, which further supports the mild anemia as being hemolytic in origin.

In the lung, WR242511-treatment induced interstitial inflammation in high dose animals. These minimal to marked changes in seven out of eight high dose animals were characterized by the infiltration of inflammatory cells and correlated with the gross observation of white or yellow foci on the apical lobes of the lung in three of eight high dose animals.

Minimal changes in clinical chemistry values (increases in AST, globulin and triglycerides in males and decreases in albumin and A/G ratio in both sexes) were seen in high dose animals. These slight alterations, without accompanying histopathologic changes, suggest that WR242511 was marginally hepatotoxic. Elevated serum haptoglobin levels, indicative of an acute phase reaction, were observed in high dose animals and mid dose males.

In summary, the primary toxic effects of WR242511 tartrate were seen in the RBCs, lungs and platelets. Although subtle, hemolytic anemia was supported by reticulocytosis, secondary splenic extramedullary hematopoiesis and bone marrow hyperplasia in high dose animals. A slight, statistically insignificant decrease in body weight (-0.6 kg) was seen in high dose males and females. Methemoglobinemia, the desired pharmacologic effect, accompanied by clinical signs of cyanosis (blue gums, tongue and sclera), and mild to moderate thrombocytopenia were observed in mid and high dose animals. WR242511-induced interstitial pulmonary inflammation was observed in seven out of eight high dose animals. Minimal, but significant increases in serum AST, globulin, and triglyceride levels in high dose males and decreases in albumin levels and A/G ratio in both high dose males and females, not accompanied by corresponding histopathologic changes in the liver, suggests that WR242511 is marginally hepatotoxic. Additionally, increased serum haptoglobin levels, indicative of an acute phase reaction, were observed in mid dose males and high dose animals. Because the aforementioned toxic responses were limited to the mid and high dose levels, the no-observed effect level (NOEL) of WR242511 tartrate was 0.1 mg base/kg/day.

6. PERSONNEL

DRAFT

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
Pathologist	Michael J. Tomlinson, D.V.M., Ph.D., D.A.C.V.P.
Histopathologist	Richard H. Bruner, D.V.M., D.A.C.V.P.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	Terry Hewett, D.V.M.
Cardiologist	Robert Hamlin, D.V.M., Ph.D., D.A.V.C.P.
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Teresa O'Neill, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Clinical Pathology	Maria Lang, A.H.T., C.V.T.
Quality Assurance	Ronald C. Schoenbeck

7. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

Table 1

FOUR WEEK ORAL DOSE TOXICITY STUDY OF WR242511 IN DOGS

DRAFT

Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.1	0.3	1.0
Dogs/Sex	4	4	4	4
Deaths	0	NE	0	0
Body Weight	NE	NE	NE	↓ (?)
Food Consumption	NE	NE	NE	●
Clinical Signs	NE	NE	Blue gums (2M/2F) Blue sclera (4M/4F) Blue tongue (4M/4F)	Blue gums (4M/4F) Blue sclera (4M/4F) Blue tongue (4M/4F)
Clinical Chemistry[a]	NE	NE	↑ HPT (M)	↑ AST (M) ↓ A/G ↓ ALB ↑ TRIG (M) ↑ GLOB (M) ↑ HPT
Hematology[b]	NE	NE	↑ METHGB ↑ MCV (F?) ↓ PLT	↓ RBC (?) ↑ RETICS ↓ HGB (?) ↑ nRBCs (F?) ↓ HCT (?) ↕ METHB ↕ MCV (?) ↓ PLT ↓ MCHC (M)(F?)
Electrocardiography	NE	NE	NE	NE
Ophthalmology	NE	NE	NE	NE
Organ Weights (% brain)	NE	NE	NE	↑ Spleen
Histopathology	NE	SPLEEN - Extramedullary hematopoiesis (1M)	NE	LUNGS - Interstitial inflammation (3M/4F) SPLEEN - Extramedullary hematopoiesis (4M/4F) BONE MARROW - Hyperplasia (4M/4F)
Conclusions	The primary toxic effects of WR242511 were seen in the RBCs, lungs and platelets. Although subtle, hemolytic anemia was supported by reticulocytosis, secondary splenic extramedullary hematopoiesis and bone marrow hyperplasia in high dose animals. A slight, statistically insignificant decrease in body weight (-0.6 kg) was seen in high dose males and females. Methemoglobinemia, the desired pharmacologic effect, accompanied by clinical signs of cyanosis (blue gums, tongue and sclera), and mild to moderate thrombocytopenia were observed in mid and high dose animals. WR242511-induced interstitial pulmonary inflammation was observed in seven out of eight high dose animals. Minimal, but significant increases in serum AST, globulin, and triglyceride levels in high dose males and decreases in albumin levels and A/G ratio in both high dose males and females, not accompanied by corresponding histopathologic changes in the liver, suggests that WR242511 is marginally hepatotoxic. Additionally, increased serum haptoglobin levels, indicative of an acute phase reaction, were observed in mid dose males and high dose animals. Because the aforementioned toxic responses were limited to the mid and high dose levels, the no-observed effect level (NOEL) of WR242511 tartrate was 0.1 mg base/kg/day.			

[a]AST = aspartate aminotransferase, ALB = albumin, GLOB = globulin, A/G = albumin/globulin ratio, TRIG = triglycerides, HPT = haptoglobin

[b]RBC = red blood cell count, HGB = hemoglobin, HCT = hematocrit, MCV = mean corpuscular volume, MCHC = mean corpuscular hemoglobin concentration, RETICS = reticulocyte count, nRBCS = nucleated red blood cells, METHB = methemoglobin, PLT = platelets

? = Possible or marginal effect NE = No effect

M = male F = female

Table 2

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 134 SEX: MALE

DOSE:(mg/kg)	0	0.1	0.3	1.0 (mg base/kg/day)
GROUP:	1-M	2-M	3-M	4-M
Blue Gums	0	0	2	4
Blue Sclera	0	0	4	4
Blue Tongue	0	0	4	4
Total Number of Animals	4	4	4	4

STUDY: 134 SEX: FEMALE

DOSE:(mg/kg)	0	0.1	0.3	1.0 (mg base/kg/day)
GROUP:	1-F	2-F	3-F	4-F
Blue Gums	0	0	2	4
Blue Sclera	0	1	4	4
Blue Tongue	0	1	4	4
Total Number of Animals	4	4	4	4

Table 3.1

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 134 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
DAY -10	MEAN	10.1	10.1	10.0	10.0
	S.D.	0.31	0.72	0.64	0.69
	N	4	4	4	4
DAY -3	MEAN	10.1	10.1	10.0	10.1
	S.D.	0.15	0.76	0.56	0.24
	N	4	4	4	4
DAY 4	MEAN	10.0	9.9	9.9	9.7
	S.D.	0.25	0.79	0.45	0.73
	N	4	4	4	4
DAY 11	MEAN	9.9	9.9	9.9	9.4
	S.D.	0.33	0.89	0.59	0.76
	N	4	4	4	4
DAY 18	MEAN	10.4	10.2	10.1	9.5
	S.D.	0.40	0.96	0.61	0.68
	N	4	4	4	4
DAY 26	MEAN	10.2	10.3	10.1	9.5
	S.D.	0.26	0.99	0.76	0.74
	N	4	4	4	4

Analysis of Variance using DUNNETT'S Procedure

Table 3.2

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 134 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
DAY -10	MEAN	8.8	9.0	8.7	8.9
	S.D.	0.40	0.31	0.46	0.67
	N	4	4	4	4
DAY -3	MEAN	8.6	8.8	9.0	9.0
	S.D.	0.57	0.34	0.43	0.89
	N	4	4	4	4
DAY 4	MEAN	8.6	8.8	8.7	8.5
	S.D.	0.67	0.37	0.69	0.63
	N	4	4	4	4
DAY 11	MEAN	8.6	8.9	8.7	8.4
	S.D.	0.70	0.36	0.70	0.68
	N	4	4	4	4
DAY 18	MEAN	8.8	9.2	9.0	8.4
	S.D.	0.90	0.37	0.66	0.78
	N	4	4	4	4
DAY 26	MEAN	8.8	9.1	9.0	8.4
	S.D.	0.86	0.43	0.68	0.69
	N	4	4	4	4

Analysis of Variance using DUNNETT'S Procedure

Table 4.1

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)[a]

STUDY: 134 SEX: MALE

PERIOD[b]	DOSE: (mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
DAY 4	MEAN	-0.2	-0.1	-0.1	-0.5
	S.D.	0.19	0.13	0.15	0.84
	N	4	4	4	4
DAY 11	MEAN	-0.1	0.0	-0.1	-0.3
	S.D.	0.17	0.14	0.21	0.24
	N	4	4	4	4
DAY 18	MEAN	0.4	0.3	0.2	0.1
	S.D.	0.10	0.10	0.21	0.18
	N	4	4	4	4
DAY 26	MEAN	-0.1	0.1	0.1	0.0
	S.D.	0.21	0.05	0.19	0.22
	N	4	4	4	4
TOTAL GAIN	MEAN	0.1	0.3	0.1	-0.6
	S.D.	0.29	0.28	0.55	0.94
	N	4	4	4	4

Analysis of Variance using DUNNETT'S Procedure

a = Successive periods

b = Baseline is Day -3

Table 4.2

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)[a]

STUDY: 134 SEX: FEMALE

PERIOD[b]	DOSE: (mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
DAY 4	MEAN	0.0	0.1	-0.3	-0.5
	S.D.	0.13	0.13	0.79	0.68
	N	4	4	4	4
DAY 11	MEAN	0.0	0.1	0.0	-0.2
	S.D.	0.05	0.13	0.10	0.13
	N	4	4	4	4
DAY 18	MEAN	0.3	0.4	0.3	0.1
	S.D.	0.37	0.21	0.16	0.13
	N	4	4	4	4
DAY 26	MEAN	0.0	-0.1	0.0	0.0
	S.D.	0.10	0.14	0.13	0.17
	N	4	4	4	4
TOTAL GAIN	MEAN	0.2	0.4	0.1	-0.6
	S.D.	0.38	0.29	0.84	0.90
	N	4	4	4	4

Analysis of Variance using DUNNETT'S Procedure

a = Successive periods

b = Baseline is Day -3

Table 5.1

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF FOOD CONSUMPTION (Grams)

STUDY: 134 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
DAY -13	MEAN	208	251	207	276
	S.D.	42.6	56.6	53.9	131.3
	N	4	4	4	4
DAY -9	MEAN	276	288	302	316
	S.D.	123.1	47.2	117.7	122.2
	N	4	4	4	4
DAY 5	MEAN	289	319	344	301
	S.D.	75.1	103.2	66.9	130.7
	N	4	4	4	4
DAY 12	MEAN	354	366	377	336
	S.D.	34.8	69.0	29.4	100.2
	N	4	4	4	4
DAY 19	MEAN	329	396	344	335
	S.D.	51.4	8.0	109.3	124.4
	N	4	4	4	4
DAY 26	MEAN	285	320	359	341
	S.D.	64.8	84.4	82.0	68.4
	N	4	4	4	4

Table 5.2

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

DRAFT

SUMMARY OF FOOD CONSUMPTION (Grams)

STUDY: 134 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
DAY -13	MEAN	211	257	203	287
	S.D.	57.1	97.3	147.1	76.3
	N	4	4	4	4
DAY -9	MEAN	243	262	311	262
	S.D.	87.0	37.4	102.2	65.6
	N	4	4	4	4
DAY 5	MEAN	319	349	308	254
	S.D.	77.3	62.9	105.1	68.3
	N	4	4	4	4
DAY 12	MEAN	296	378	308	300
	S.D.	121.1	43.5	87.3	60.5
	N	4	4	4	4
DAY 19	MEAN	278	342	350	302
	S.D.	88.8	70.1	66.3	76.9
	N	4	4	4	4
DAY 26	MEAN	336	291	318	359
	S.D.	43.3	90.1	49.6	47.9
	N	4	4	4	4

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 134
STUDY NO: 134
ABBR: ALT

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	33	28	27	35
SD	12.9	8.4	8.1	5.7
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	36	34	33	36
SD	8.6	9.0	7.4	8.4
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	44	27	31	33
SD	18.8	4.3	3.9	2.2
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	40	34	33	35
SD	9.3	6.6	6.2	6.4
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 134
STUDY NO: 134
ABBR: ALT

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	32	29	31	32
SD	10.0	6.7	7.2	6.3
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	41	35	33	45
SD	17.6	8.5	9.5	7.1
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	36	31	45	36
SD	9.2	8.3	16.1	8.1
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	37	36	37	32
SD	8.8	9.8	11.6	9.9
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY ID: 134
STUDY NO: 134
ABBR: AST

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	32	33	32	40
SD	2.8	0.6	4.6	2.6
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	31	33	38	39
SD	5.7	4.0	4.3	6.4
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	31	31	40	42
SD	3.3	2.1	6.7	4.3
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	34	36	43	55*
SD	4.3	5.7	4.5	7.8
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY ID: 134
STUDY NO: 134
ABBR: AST

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	33	33	37	43
SD	4.7	6.2	9.0	5.4
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	33	36	39	38
SD	4.6	6.6	8.1	4.1
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	32	35	49	42
SD	7.0	3.0	16.0	6.1
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	31	40	50	41
SD	6.4	10.9	8.8	3.7
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 134
STUDY NO: 134
ABBR: TP

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	6.3	6.1	6.5	6.6
SD	0.24	0.30	0.37	0.21
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	6.2	6.4	6.7	6.5
SD	0.51	0.25	0.26	0.30
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	5.9	6.1	6.4	6.5
SD	0.38	0.13	0.30	0.17
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	6.0	6.1	6.6	6.7
SD	0.48	0.50	0.56	0.29
N	4	4	4	4

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DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 134
STUDY NO: 134
ABBR: TP

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	6.2	5.9	6.9	6.2
SD	0.51	0.41	0.60	0.44
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	6.1	6.0	6.8	6.6
SD	0.22	0.35	0.44	0.26
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	5.9	6.2	6.8	6.4
SD	0.44	0.10	0.48	0.17
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	6.1	6.0	6.5	6.3
SD	0.25	0.32	0.15	0.19
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 134
STUDY NO: 134
ABBR: ALB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	3.3	3.3	3.1	3.5
SD	0.13	0.19	0.14	0.13
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	3.4	3.3	3.3	3.4
SD	0.34	0.17	0.17	0.14
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	3.3	3.3	3.2	3.3
SD	0.19	0.06	0.10	0.10
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	3.2	3.1	3.3	3.0*
SD	0.21	0.22	0.26	0.17
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 134
STUDY NO: 134
ABBR: ALB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	3.2	3.1	3.2	3.3
SD	0.25	0.22	0.16	0.15
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	3.2	3.2	3.3	3.4
SD	0.25	0.10	0.19	0.00
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	3.2	3.2	3.3	3.4
SD	0.18	0.08	0.17	0.05
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	3.2	3.2	3.2	2.9*
SD	0.26	0.10	0.08	0.17
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

Table 6.9

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 134
STUDY NO: 134
ABBR: GLOB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	3.0	2.8	3.4	3.1
SD	0.24	0.28	0.40	0.18
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	2.8	3.1	3.5	3.1
SD	0.17	0.35	0.24	0.17
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	2.6	2.8	3.3	3.2
SD	0.21	0.17	0.30	0.13
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	2.8	3.0	3.3	3.7*
SD	0.33	0.33	0.65	0.22
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

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SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 134
STUDY NO: 134
ABBR: GLOB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	2.9	2.8	3.7	2.9
SD	0.26	0.19	0.44	0.31
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	2.9	2.8	3.4	3.2
SD	0.13	0.29	0.51	0.26
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	2.7	3.0	3.5	3.0
SD	0.28	0.17	0.41	0.14
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	2.9	2.8	3.3	3.4
SD	0.05	0.36	0.17	0.13
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 134
STUDY NO: 134
ABBR: A/G

SEX: MALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	1.13	1.19	0.94	1.12
SD	0.108	0.152	0.137	0.085
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	1.25	1.07	0.95	1.11
SD	0.064	0.186	0.090	0.037
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	1.24	1.16	0.97	1.06
SD	0.058	0.090	0.090	0.050
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	1.17	1.02	1.04	0.80*
SD	0.119	0.085	0.265	0.063
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 134
STUDY NO: 134
ABBR: A/G

SEX: FEMALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	1.11	1.13	0.88	1.15
SD	0.034	0.019	0.071	0.077
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	1.09	1.13	0.99	1.08
SD	0.112	0.112	0.179	0.088
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	1.20	1.06	0.97	1.13
SD	0.069	0.088	0.120	0.047
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	1.12	1.17	0.98	0.88*
SD	0.097	0.163	0.067	0.069
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bilirubin

STUDY ID: 134
STUDY NO: 134
ABBR: TBILI

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.14	0.13	0.13	0.17
SD	0.010	0.029	0.026	0.018
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.14	0.13	0.13	0.17
SD	0.008	0.010	0.008	0.026
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.13	0.13	0.17	0.18
SD	0.018	0.019	0.040	0.042
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.13	0.11	0.14	0.16
SD	0.013	0.014	0.010	0.015
N	4	4	4	4

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bilirubin

STUDY ID: 134
STUDY NO: 134
ABBR: TBILI

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.12	0.13	0.14	0.15
SD	0.019	0.026	0.026	0.010
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.12	0.13	0.17	0.19
SD	0.017	0.031	0.026	0.034
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.13	0.14	0.20	0.21*
SD	0.029	0.026	0.076	0.048
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.14	0.14	0.24	0.15
SD	0.022	0.024	0.091	0.016
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 134
STUDY NO: 134
ABBR: ALKP

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	138	132	136	133
SD	17.0	8.4	15.9	27.2
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	199*	200*	196*	157
SD	52.0	49.3	47.7	31.1
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	124	113	115	93
SD	21.2	28.8	25.0	20.1
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	120	119	121	117
SD	18.7	27.1	19.0	26.7
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 134
STUDY NO: 134
ABBR: ALKP

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	120	111	118	98
SD	19.8	21.6	16.4	29.1
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	196	169	179	155
SD	118.4	92.5	77.9	84.3
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	117	114	124	92
SD	21.8	15.3	19.3	15.7
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	107	106	105	99
SD	17.0	11.4	17.5	10.0
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Gamma Glutamyl Transferase

STUDY ID: 134
STUDY NO: 134
ABBR: GGT

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	4	3	4	4
SD	1.3	1.3	1.3	1.3
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	4	4	4	3
SD	1.0	0.6	0.5	0.8
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	3	3	4	5
SD	0.8	0.8	1.7	1.3
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	4	3	5	3
SD	1.0	1.3	0.6	1.2
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Gamma Glutamyl Transferase

STUDY ID: 134
STUDY NO: 134
ABBR: GGT

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	4	3	3	4
SD	1.7	0.8	1.5	1.7
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	4	4	4	3
SD	2.5	1.3	2.4	1.9
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	3	3	4	2
SD	1.4	0.6	1.7	1.0
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	4	3	4	3
SD	0.6	0.6	0.5	1.0
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 134
STUDY NO: 134
ABBR: CHOL

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	199	184	186	185
SD	38.8	27.8	6.1	10.4
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	185	191	191	187
SD	30.7	34.3	14.8	14.0
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	182	196	197	188
SD	22.7	23.8	27.7	26.9
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	183	174	209	215
SD	34.5	33.5	34.8	37.7
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 134
STUDY NO: 134
ABBR: CHOL

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	182	172	202	183
SD	34.0	26.8	29.9	47.6
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	157	160	169	173
SD	29.2	29.8	34.7	38.8
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	158	162	184	182
SD	4.3	11.2	31.9	28.3
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	181	185	207	199
SD	35.7	27.2	44.4	43.2
N	4	4	4	4

LABCAT CC4.25

Table 6.21

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 134
STUDY NO: 134
ABBR: TRY

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	41	45	35	32
SD	8.2	11.9	9.6	10.4
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	42	33	31	31
SD	6.5	4.7	6.7	7.2
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	38	40	48	35
SD	4.3	7.0	21.3	5.0
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	39	36	44	55*
SD	7.0	13.1	10.4	9.1
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 134
STUDY NO: 134
ABBR: TRY

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	40	41	47	39
SD	7.3	8.5	5.0	6.6
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	40	34	47	39
SD	15.4	14.4	8.7	9.8
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	36	42	68	43
SD	5.0	8.4	27.7	8.7
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	35	50	58	41
SD	7.1	12.0	15.3	7.0
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY ID: 134
STUDY NO: 134
ABBR: LDH

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	72	47	51	70
SD	30.7	17.3	19.6	21.4
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	69	63	79	114
SD	28.8	26.5	35.4	98.9
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	52	59	78	62
SD	8.7	22.5	64.8	16.1
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	54	64	58	145
SD	10.8	13.4	13.6	32.9
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY ID: 134
STUDY NO: 134
ABBR: LDH

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	93	107	111	172
SD	71.7	48.4	87.6	147.0
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	62	76	88	86
SD	35.9	34.0	32.2	31.0
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	61	77	97	104
SD	45.3	31.0	45.6	62.6
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	56	97	109	96
SD	12.7	32.8	78.5	46.5
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 134
STUDY NO: 134
ABBR: CK

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	337	210	191	205
SD	185.1	70.4	28.9	87.1
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	206	213	234	234
SD	40.7	67.7	61.9	140.3
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	172	171	216	153
SD	46.1	77.7	102.5	33.2
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	211	208	138	212
SD	60.5	54.0	15.0	104.3
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 134
STUDY NO: 134
ABBR: CK

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	220	241	218	399
SD	65.0	56.6	71.9	258.0
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	171	211	243	170
SD	42.2	67.7	92.9	18.5
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	226	201	245	192
SD	85.9	62.4	87.6	56.7
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	166	357	182	125
SD	14.0	203.5	49.4	35.1
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 134
STUDY NO: 134
ABBR: BUN

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	13.7	14.9	13.9	13.5
SD	2.46	2.23	2.09	1.80
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	14.8	15.0	15.3	18.0
SD	1.97	0.92	0.74	4.20
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	13.0	13.3	13.6	16.1
SD	3.73	2.45	1.65	3.15
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	15.6	15.2	14.2	15.9
SD	2.34	2.88	0.82	2.96
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 134
STUDY NO: 134
ABBR: BUN

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	14.5	14.1	16.0	15.4
SD	2.77	3.00	4.34	2.64
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	13.2	12.9	15.5	18.1
SD	2.81	0.93	2.05	2.62
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	12.2	11.5	14.6	15.2
SD	2.22	1.61	3.24	3.80
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	14.5	14.4	16.2	16.5
SD	2.79	1.53	2.96	2.43
N	4	4	4	4

LABCAT CC4.25

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 134
STUDY NO: 134
ABBR: CREA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.70	0.76	0.77	0.77
SD	0.083	0.088	0.071	0.031
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.74	0.79	0.82	0.85
SD	0.065	0.086	0.112	0.087
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.72	0.69	0.78	0.79
SD	0.066	0.021	0.042	0.022
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.69	0.72	0.81	0.80
SD	0.082	0.079	0.083	0.055
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 134
STUDY NO: 134
ABBR: CREA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.73	0.68	0.71	0.72
SD	0.069	0.032	0.090	0.123
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.70	0.72	0.76	0.75
SD	0.076	0.025	0.048	0.077
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.71	0.73	0.78	0.75
SD	0.034	0.040	0.124	0.062
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.71	0.68	0.79	0.74
SD	0.064	0.046	0.083	0.068
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 134
STUDY NO: 134
ABBR: NA

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	144	145	144	143
SD	1.7	0.6	1.4	1.4
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	144	146	145	146
SD	1.0	1.2	1.6	1.0
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	144	145	144	144
SD	0.8	0.6	1.6	1.7
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	144	146	145	145
SD	1.8	2.5	2.7	1.5
N	4	4	4	4

LABCAT CC4.25

Table 6.32

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 134
STUDY NO: 134
ABBR: NA

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	144	145	146	144
SD	2.4	1.0	1.7	1.0
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	144	144	145	145
SD	0.5	1.0	1.7	0.6
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	144	144	144	144
SD	1.9	2.2	1.0	1.8
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	144	144	144	144
SD	1.9	1.3	0.5	0.5
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 134
STUDY NO: 134
ABBR: K

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	4.79	4.68	4.67	4.33
SD	0.216	0.185	0.330	0.230
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	4.50	4.54	4.35	4.63
SD	0.143	0.145	0.153	0.605
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	4.46	4.41	4.44	4.25
SD	0.156	0.268	0.420	0.206
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	4.55	4.65	4.40	4.37
SD	0.209	0.176	0.241	0.371
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 134
STUDY NO: 134
ABBR: K

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	4.51	4.48	4.31	4.46
SD	0.458	0.286	0.269	0.203
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	4.59	4.59	4.37	4.36
SD	0.261	0.286	0.296	0.177
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	4.41	4.53	4.42	4.47
SD	0.330	0.262	0.140	0.332
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	4.40	4.37	4.31	4.25
SD	0.220	0.273	0.304	0.298
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 134
STUDY NO: 134
ABBR: CL

SEX: MALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	121	119	116	118
SD	3.7	4.9	1.0	2.2
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	119	120	115	118
SD	5.2	3.2	1.0	3.0
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	116	118	116	116
SD	2.5	6.3	0.5	2.8
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	120	121	117	119
SD	2.2	7.5	4.6	1.9
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 134
STUDY NO: 134
ABBR: CL

SEX: FEMALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	118	120	119	117
SD	3.3	2.1	3.1	1.7
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	119	120	115	117
SD	2.2	7.2	3.3	2.2
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	116	120	118	116
SD	2.9	7.9	1.3	2.6
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	118	122	118	116
SD	3.3	2.5	1.7	2.2
N	4	4	4	4

LABCAT CC4.25

Table 6.37

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 134
STUDY NO: 134
ABBR: CA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	11.1	10.9	10.8	10.6
SD	0.37	0.19	0.36	0.22
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	11.3	11.0	10.9	10.8
SD	0.39	0.54	0.21	0.13
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	11.1	10.6	10.6	10.7
SD	0.36	0.37	0.24	0.13
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	10.8	10.6	10.6	10.5
SD	0.22	0.34	0.29	0.25
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 134
STUDY NO: 134
ABBR: CA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	11.0	10.7	10.5	10.6
SD	0.41	0.36	0.14	0.41
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	11.2	10.6	10.7	10.9
SD	0.26	0.13	0.22	0.15
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	11.0	10.6	10.7	10.8
SD	0.21	0.17	0.34	0.31
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	11.0	10.6	10.5	10.4
SD	0.46	0.41	0.27	0.37
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 134
STUDY NO: 134
ABBR: IP

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	6.1	6.6	6.5	5.8
SD	0.47	0.48	0.10	0.22
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	6.0	6.3	6.0	5.7
SD	0.62	0.72	0.66	0.13
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	5.5	6.1	5.5	6.0
SD	0.24	0.54	0.89	0.34
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	5.8	5.9	6.0	5.3
SD	0.53	0.70	0.33	0.52
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 134
STUDY NO: 134
ABBR: IP

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	5.6	5.3	5.7	5.4
SD	0.99	0.49	0.66	0.79
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	5.1	6.0	5.8	5.0
SD	0.74	0.78	0.44	0.96
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	5.2	5.5	4.9	4.6
SD	0.44	0.98	0.78	0.40
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	5.6	5.5	5.5	5.6
SD	0.42	0.82	0.57	0.39
N	4	4	4	4

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 134
STUDY NO: 134
ABBR: GLU

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	121	112	117	122
SD	6.0	7.0	10.1	9.0
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	119	114	111	112
SD	3.0	12.4	5.9	3.4
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	108	105	110	111
SD	11.6	12.0	4.0	7.4
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	113	1D6	109	110
SD	11.1	15.9	5.7	8.9
N	4	4	4	4

LABCAT CC4.25

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 134
STUDY NO: 134
ABBR: GLU

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	116	105	107	103
SD	18.0	8.1	12.3	12.7
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	116	101	106	103
SD	10.6	12.0	12.3	6.1
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	119	114	120	115
SD	5.2	4.1	4.4	9.7
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	116	110	109	107
SD	7.4	15.4	11.7	5.9
N	4	4	4	4

LABCAT CC4.25

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Haptoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: HAPT

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	62.2	67.5	62.7	56.4
SD	20.58	16.13	9.02	23.23
N	4	4	3	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	43.5	55.1	62.8	51.4
SD	14.48	8.60	16.95	9.58
N	4	3	3	3
Group: 3-M : 0.3 mg base/kg/day				
MEAN	81.1	104.3*	82.9	115.0*
SD	35.72	16.80	29.26	27.70
N	4	4	3	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	76.4	96.4*	125.6	259.9*
SD	12.46	6.33	51.95	3.77
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT CC4.3

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Haptoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: HAPT

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	56.1	92.5	76.8	63.5
SD	34.58	NA	NA	60.88
N	4	1	1	2
Group: 2-F : 0.1 mg base/kg/day				
MEAN	88.4	65.9	71.5	17.2
SD	85.98	43.64	3.68	NA
N	3	3	2	1
Group: 3-F : 0.3 mg base/kg/day				
MEAN	17.1	80.0	35.5	NA
SD	NA	6.29	NA	NA
N	1	2	1	0
Group: 4-F : 1.0 mg base/kg/day				
MEAN	52.5	50.4	46.3	202.9*
SD	24.81	NA	34.12	46.24
N	3	1	3	4

*-Significant Difference from Control P < .05 NA-Not Applicable

LABCAT CC4.3

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY IO: 134
STUDY NO: 134
ABBR: RBC

SEX: MALE

UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	6.19	6.39	6.24	6.51
SD	0.547	0.267	0.787	0.495
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	6.11	6.18	6.20	5.86
SD	0.223	0.442	0.478	0.350
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	6.37	6.22	6.32	6.01
SD	0.329	0.401	0.157	0.433
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	6.19	6.06	6.24	5.74
SD	0.600	0.566	0.650	0.603
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY ID: 134
STUDY NO: 134
ABBR: RBC

SEX: FEMALE

UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	6.41	6.32	6.38	6.06
SD	0.530	0.136	0.316	0.347
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	6.55	6.10	6.45	6.24
SD	0.752	0.389	0.684	0.379
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	6.50	6.27	6.54	5.88
SD	0.192	0.110	0.369	0.137
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	6.50	6.57	6.52	5.47
SD	0.432	0.102	0.492	0.426
N	4	4	4	4

LABCAT HE4.26

Table 7.3

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: HGB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	15.2	15.6	15.4	15.8
SD	0.98	0.32	1.61	1.06
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	14.9	15.0	15.0	13.9
SD	0.70	1.05	1.19	1.06
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	15.8	15.3	15.7	14.8
SD	0.80	0.91	0.10	0.87
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	15.1	14.8	15.4	13.9
SD	1.38	1.30	1.53	1.35
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: HGB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	15.9	15.5	15.8	14.6
SD	1.59	0.75	0.91	0.65
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	16.3	15.0	16.1	15.3
SD	1.82	0.83	1.95	1.26
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	16.3	15.7	16.4	14.8
SD	0.57	0.45	0.66	0.21
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	15.9	16.0	16.0	13.4
SD	0.81	0.63	0.99	1.06
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 134
STUDY NO: 134
ABBR: HCT

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	43.8	45.1	43.9	45.5
SD	2.99	1.18	5.00	2.25
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	42.3	42.5	42.6	40.2
SD	1.89	2.83	3.27	3.06
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	45.0	43.6	44.4	42.8
SD	2.44	2.33	0.22	2.38
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	43.6	42.5	43.9	41.9
SD	3.75	3.70	4.39	3.66
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 134
STUDY NO: 134
ABBR: HCT

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	45.3	44.4	44.8	42.3
SD	4.74	1.92	2.79	2.11
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	46.1	42.6	45.8	44.0
SD	4.93	2.33	4.94	3.57
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	46.8	44.7	47.0	43.1
SD	1.86	1.07	1.84	0.57
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	44.8	45.2	45.1	40.0
SD	2.04	1.63	2.68	2.86
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 134
STUDY NO: 134
ABBR: MCV

SEX: MALE

UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	70.8	70.7	70.5	70.0
SD	1.79	2.12	1.89	2.63
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	69.2	68.8	68.7	68.6
SD	0.83	0.35	0.22	1.62
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	70.6	70.3	70.3	71.3
SD	1.56	1.42	1.58	1.75
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	70.6	70.1	70.4	73.0
SD	0.96	0.71	0.79	2.03
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 134
STUDY NO: 134
ABBR: MCV

SEX: FEMALE

UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	70.6	70.2	70.2	69.9
SD	1.97	1.65	1.48	1.14
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	70.4	69.9	70.3	70.3
SD	1.44	1.69	1.68	1.73
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	72.0	71.3	72.0	73.4
SD	1.91	1.59	1.75	2.08
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	69.1	68.7	69.3	73.1
SD	3.15	2.59	2.10	2.74
N	4	4	4	4

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemo.

STUDY ID: 134
STUDY NO: 134
ABBR: MCH

SEX: MALE

UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	24.5	24.4	24.7	24.3
SD	0.65	0.78	0.98	0.85
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	24.4	24.3	24.2	23.6
SD	0.35	0.08	0.17	0.67
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	24.8	24.6	24.8	24.6
SD	0.39	0.53	0.62	0.35
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	24.4	24.4	24.6	24.3
SD	0.26	0.15	0.27	0.33
N	4	4	4	4

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemo.

STUDY ID: 134
STUDY NO: 134
ABBR: MCH

SEX: FEMALE

UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	24.8	24.6	24.8	24.2
SD	0.54	0.70	0.65	0.49
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	24.8	24.6	24.7	24.4
SD	0.57	0.74	0.52	0.79
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	25.0	25.0	25.1	25.2
SD	0.36	0.54	0.60	0.38
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	24.5	24.3	24.6	24.5
SD	1.42	0.92	0.76	0.41
N	4	4	4	4

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpus. Hemo. Conc.

STUDY ID: 134
STUDY NO: 134
ABBR: MCHC

SEX: MALE

UNITS: g/dl

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	34.7	34.6	35.0	34.7
SD	0.42	0.71	0.66	0.73
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	35.3	35.4	35.3	34.5
SD	0.29	0.13	0.19	0.37
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	35.2	35.0	35.3	34.5
SD	0.44	0.34	0.24	0.57
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	34.6	34.8	35.0	33.3*
SD	0.37	0.19	0.35	0.56
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpus. Hemo. Conc.

STUDY ID: 134
STUDY NO: 134
ABBR: MCHC

SEX: FEMALE

UNITS: g/dl

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	35.2	35.0	35.2	34.6
SD	0.38	0.37	0.41	0.22
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	35.3	35.2	35.2	34.7
SD	0.25	0.19	0.51	0.46
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	34.8	35.1	34.9	34.3
SD	0.57	0.37	0.22	0.69
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	35.4	35.4	35.6	33.5
SD	0.68	0.45	0.49	1.18
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocytes

STUDY ID: 134
STUDY NO: 134
ABBR: RETICS

SEX: MALE

UNITS: %RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.3	0.2	0.2	0.2
SD	0.15	0.19	0.24	0.16
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.2	0.1	0.1	0.2
SD	0.10	0.05	0.10	0.05
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.4	0.4	0.5	0.5
SD	0.17	0.22	0.25	0.35
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.3	0.3	0.4	1.1*
SD	0.18	0.30	0.24	0.46
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocytes

STUDY ID: 134
STUDY NO: 134
ABBR: RETICS

SEX: FEMALE

UNITS: %RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.3	0.2	0.3	0.2
SD	0.26	0.05	0.21	0.27
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.3	0.2	0.5	0.4
SD	0.48	0.13	0.26	0.24
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.4	0.4	0.4	0.5
SD	0.31	0.19	0.17	0.14
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.3	0.4	0.8*	1.1*
SD	0.06	0.13	0.17	0.43
N	4	4	4	4

*-Significant Difference from Control $P < .05$

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUDY ID: 134
STUDY NO: 134
ABBR: NRBC

SEX: MALE

UNITS: #/100 WBC

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.3
SD	0.00	0.00	0.00	0.50
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.3

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUDY ID: 134
STUDY NO: 134
ABBR: NRBC

SEX: FEMALE

UNITS: #/100 WBC

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.3
SD	0.00	0.00	0.00	0.50
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.0	0.0	1.3	1.5
SD	0.00	0.00	1.89	2.38
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.3

Table 7.17

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 134
STUDY NO: 134
ABBR: HB

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.0	0.0	0.1	0.1
SD	0.00	0.00	0.10	0.15
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.0	0.1	0.0	0.2
SD	0.00	0.10	0.00	0.19
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.0	0.1	0.1	0.1
SD	0.05	0.14	0.10	0.10
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.0	0.0	0.2	0.2
SD	0.00	0.00	0.13	0.29
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 134
STUDY NO: 134
ABBR: HB

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.0	0.0	0.1	0.0
SD	0.00	0.00	0.10	0.00
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.0	0.0	0.2	0.0
SD	0.00	0.00	0.13	0.00
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.0	0.0	0.2	0.1
SD	0.05	0.00	0.15	0.15
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.1	0.1	0.3	0.2
SD	0.06	0.20	0.38	0.24
N	4	4	4	4

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: %METHGB

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Day 0	Week 2	Week 3	Week 4	Week 5
Group: 1-M : 0 mg base/kg/day							
MEAN	1.1	1.0	0.9	1.3	1.3	1.0	1.3
SD	0.25	0.21	0.10	0.31	0.51	0.47	0.71
N	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day							
MEAN	1.0	0.9	0.9	1.4	2.4	2.6	2.4
SD	0.13	0.22	0.27	0.43	1.06	1.06	0.83
N	4	4	4	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day							
MEAN	1.0	0.9	1.0	6.2*	8.6*	8.5*	8.1*
SD	0.24	0.13	0.13	2.78	1.43	1.67	1.82
N	4	4	4	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day							
MEAN	1.0	1.0	1.0	24.7*	27.2*	26.6*	25.7*
SD	0.13	0.19	0.14	4.23	3.20	2.27	3.30
N	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT HE4.3

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 134
STUDY NO: 134
ABBR: %METHGB

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Day 0	Week 2	Week 3	Week 4	Week 5
Group: 1-F : 0 mg base/kg/day							
MEAN	0.9	0.8	0.9	0.8	1.0	0.9	1.1
SD	0.24	0.16	0.15	0.17	0.17	0.41	0.28
N	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day							
MEAN	1.2	0.9	0.7	1.9	2.2	2.3	2.3
SD	0.78	0.31	0.13	0.81	0.64	0.52	0.14
N	4	4	4	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day							
MEAN	0.8	0.9	0.9	7.4	10.0*	9.3*	8.0*
SD	0.22	0.24	0.21	3.39	2.91	2.20	1.25
N	4	4	4	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day							
MEAN	0.8	0.9	0.9	26.9*	29.4*	25.3*	23.5*
SD	0.08	0.17	0.22	9.05	7.23	5.98	6.24
N	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT HE4.3

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 134
STUDY NO: 134
ABBR: WBC

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	7.0	8.1	7.3	8.5
SD	2.13	2.07	1.88	2.22
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	6.8	8.2	8.3	7.4
SD	1.37	1.98	1.23	1.82
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	9.2	11.4	8.9	9.0
SD	0.89	4.58	1.04	1.20
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	8.1	8.3	8.3	9.1
SD	0.61	1.17	2.42	1.35
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 134
STUDY NO: 134
ABBR: WBC

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	10.0	9.0	8.8	8.5
SD	2.63	1.58	1.42	1.31
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	9.0	10.7	10.7	7.3
SD	0.65	3.45	2.17	1.16
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	7.7	9.9	9.0	8.1
SD	1.08	1.78	0.77	1.38
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	9.5	8.9	10.4	8.2
SD	3.24	1.60	3.02	1.28
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 134
STUDY NO: 134
ABBR: M. Neutrop

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	4.0	4.7	4.0	5.7
SD	1.40	1.16	1.17	1.97
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	3.9	5.4	5.0	4.3
SD	0.84	1.74	0.82	1.22
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	5.9*	7.6	5.9	6.0
SD	0.37	3.14	1.28	1.54
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	5.6	5.6	5.0	6.3
SD	0.90	0.85	2.03	1.22
N	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

LABCAT HE4.26

Table 7.24

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 134
STUDY NO: 134
ABBR: M. Neutrop

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	6.5	5.6	6.0	5.6
SD	1.86	0.94	1.03	1.53
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	6.2	7.5	7.6	4.9
SD	0.56	3.20	1.41	1.08
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	4.5	6.5	6.6	4.8
SD	0.87	1.66	0.31	1.06
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	5.8	5.2	7.1	4.9
SD	2.26	1.40	2.79	1.53
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY ID: 134
STUDY NO: 134
ABBR: I. Neutrop

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.3	0.2	0.2	0.1
SD	0.12	0.05	0.06	0.08
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.3	0.3	0.1	0.2
SD	0.10	0.10	0.10	0.08
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.7*	0.4	0.2	0.3
SD	D.22	0.17	0.10	0.17
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.4	0.3	0.3	0.3
SD	0.21	0.17	0.10	0.08
N	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

LABCAT HE4.26

Table 7.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY ID: 134
STUDY NO: 134
ABBR: I. Neutrop

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.2	0.2	0.1	0.3
SD	0.22	0.14	0.05	0.13
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.3	0.1	0.4	0.1
SD	0.24	0.10	0.19	0.08
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.2	0.2	0.1	0.0
SD	0.15	0.21	0.15	0.05
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.3	0.2	0.3	0.3
SD	0.15	0.17	0.22	0.24
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Lymphocyte

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	2.5	2.6	2.6	2.2
SD	0.75	1.15	1.13	0.75
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	2.0	2.0	2.7	2.3
SD	0.41	0.41	0.75	0.72
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	1.9	2.3	2.2	1.6
SD	1.04	0.64	1.08	0.94
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	1.6	1.7	1.9	1.4
SD	0.14	0.56	0.05	0.52
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Lymphocyte

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	2.6	2.3	2.1	1.9
SD	1.09	0.41	0.82	0.23
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	2.0	2.5	2.1	1.8
SD	0.70	0.81	1.09	0.38
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	2.4	2.6	1.9	2.6
SD	0.33	0.19	0.70	1.02
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	3.1	2.8	2.1	1.8
SD	1.05	0.50	0.36	0.77
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

Table 7.29

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Monocytes

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.1	0.3	0.3	0.3
SD	0.00	0.13	0.13	0.37
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.4	0.3	0.2	0.2
SD	0.26	0.31	0.22	0.20
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.4	0.8	0.3	0.7
SD	0.28	0.84	0.18	0.22
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.4	0.5	0.8*	0.7
SD	0.31	0.52	0.30	0.29
N	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Monocytes

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.5	0.4	0.3	0.3
SD	0.36	0.21	0.15	0.15
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.5	0.4	0.3	0.3
SD	0.42	0.19	0.14	0.19
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.3	0.2	0.5	0.4
SD	0.08	0.05	0.47	0.17
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.3	0.4	0.7	0.8
SD	0.21	0.14	0.38	0.52
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 134
STUDY NO: 134
ABBR: Eosinophil

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.2	0.4	0.2	0.2
SD	0.06	0.15	0.14	0.22
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.3	0.2	0.3	0.2
SD	0.17	0.13	0.14	0.13
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.3	0.4	0.2	0.2
SD	0.17	0.24	0.24	0.19
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.2	0.2	0.2	0.3
SD	0.08	0.22	0.15	0.24
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 134
STUDY NO: 134
ABBR: Eosinophil

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.2	0.2	0.2	0.2
SD	0.14	0.10	0.14	0.14
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.1	0.2	0.2	0.2
SD	0.10	0.06	0.14	0.15
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.2	0.2	0.1	0.2
SD	0.08	0.26	0.10	0.08
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.2	0.1	0.1	0.2
SD	0.24	0.05	0.10	0.19
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 134
STUDY NO: 134
ABBR: Basophils

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.05	0.00	0.00
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.0	0.0	0.2	0.0
SD	0.00	0.00	0.35	0.00
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 134
STUDY NO: 134
ABBR: Basophils

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.05	0.00	0.00	0.00
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.1	0.0	0.0	0.0
SD	0.20	0.00	0.00	0.00
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.0	0.0	0.0	0.0
SD	0.00	0.00	0.00	0.00
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Atypical Lymphocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Atypical L

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	0.0	0.0	0.2	0.1
SD	0.05	0.05	0.17	0.05
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	0.1	0.1	0.0	0.3
SD	0.06	0.10	0.05	0.19
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	0.2	0.1	0.2	0.3
SD	0.13	0.10	0.21	0.25
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	0.0	0.1	0.0	0.2
SD	0.05	0.08	0.05	0.21
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

Table 7.36

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Atypical Lymphocytes

STUDY ID: 134
STUDY NO: 134
ABBR: Atypical L

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	0.1	0.2	0.1	0.2
SD	0.06	0.17	0.13	0.18
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	0.1	0.1	0.1	0.2
SD	0.10	0.14	0.20	0.08
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	0.1	0.2	0.1	0.2
SD	0.06	0.06	0.06	0.14
N	4	4	3	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	0.0	0.2	0.2	0.3
SD	0.00	0.13	0.21	0.22
N	4	4	4	4

WBC corrected for NRBC = or > 10

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Platelets

STUDY ID: 134
STUDY NO: 134
ABBR: PLT

SEX: MALE

UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	322	300	279	304
SD	33.1	20.8	39.8	36.0
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	364	372	348	321
SD	68.9	36.7	68.0	38.0
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	294	260	190	127*
SD	54.6	33.4	21.0	29.3
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	372	302	142*	136*
SD	45.5	84.5	73.1	36.1
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT HE4.26

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Prothrombin Time

STUDY ID: 134
STUDY NO: 134
ABBR: PT

SEX: MALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	7.1	7.1	7.1	7.4
SD	0.14	0.24	0.17	0.26
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	7.5*	7.5	7.4	7.6
SD	0.35	0.34	0.38	0.36
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	7.0	6.9	7.0	7.1
SD	0.10	0.18	0.13	0.13
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	7.0	6.9	6.8	7.0
SD	0.13	0.14	0.10	0.13
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Prothrombin Time

STUDY ID: 134
STUDY NO: 134
ABBR: PT

SEX: FEMALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	7.1	7.1	8.1	7.4
SD	0.22	0.10	2.09	0.15
N	4	3	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	7.3	7.3	7.1	7.5
SD	0.40	0.18	0.12	0.13
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	7.3	7.0	7.0	7.2
SD	0.15	0.22	0.18	0.06
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	7.4	7.3	7.0	7.1*
SD	0.15	0.31	0.21	0.17
N	4	4	4	4

*-Significant Difference from Control P < .05

LABCAT HE4.26

Table 7.41

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FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 134
STUDY NO: 134
ABBR: APTT

SEX: MALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-M : 0 mg base/kg/day				
MEAN	11.5	11.4	11.1	11.4
SD	0.32	0.31	0.41	0.63
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	12.0	11.8	11.9	11.8
SD	0.35	0.38	0.68	1.33
N	4	4	4	4
Group: 3-M : 0.3 mg base/kg/day				
MEAN	12.6	12.2	12.1	12.2
SD	0.83	0.40	0.53	0.57
N	4	4	4	4
Group: 4-M : 1.0 mg base/kg/day				
MEAN	12.0	12.0	11.6	12.3
SD	0.51	0.48	0.57	0.85
N	4	4	4	4

LABCAT HE4.26

DRAFT

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF HEMATOLOGY TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 134
STUDY NO: 134
ABBR: APTT

SEX: FEMALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Wk -2/-1	Week 2	Week 5
Group: 1-F : 0 mg base/kg/day				
MEAN	12.0	11.6	10.8	12.2
SD	0.94	0.30	2.78	1.23
N	4	3	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	12.4	12.0	11.9	12.0
SD	0.90	0.51	1.02	1.07
N	4	4	4	4
Group: 3-F : 0.3 mg base/kg/day				
MEAN	12.1	12.1	11.7	12.1
SD	0.36	0.85	0.66	0.78
N	4	4	4	4
Group: 4-F : 1.0 mg base/kg/day				
MEAN	12.2	11.8	11.8	12.4
SD	0.37	0.26	0.66	0.84
N	4	4	4	4

LABCAT HE4.26

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF URINALYSIS TESTS
TEST: pH

STUDY ID: 134
STUDY NO: 134
ABBR: PH

SEX: MALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s): Week 5

Group: 1-M : 0 mg base/kg/day	
MEAN	7.3
SD	0.50
N	4
Group: 2-M : 0.1 mg base/kg/day	
MEAN	6.8
SD	0.96
N	4
Group: 3-M : 0.3 mg base/kg/day	
MEAN	6.0*
SD	0.00
N	4
Group: 4-M : 1.0 mg base/kg/day	
MEAN	6.0*
SD	0.00
N	4

*-Significant Difference from Control P < .05

LABCAT CC4.3

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF URINALYSIS TESTS
TEST: pH

STUDY ID: 134
STUDY NO: 134
ABBR: PH

SEX: FEMALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s): Week 5

Group: 1-F : 0 mg base/kg/day	
MEAN	6.0
SD	0.00
N	4
Group: 2-F : 0.1 mg base/kg/day	
MEAN	6.3
SD	0.50
N	4
Group: 3-F : 0.3 mg base/kg/day	
MEAN	6.3
SD	0.50
N	4
Group: 4-F : 1.0 mg base/kg/day	
MEAN	6.0
SD	0.00
N	4

LABCAT CC4.3

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF URINALYSIS TESTS
TEST: Specific Gravity

STUDY ID: 134
STUDY NO: 134
ABBR: SG

SEX: MALE

UNITS: mg/mL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s): Week 5

Group: 1-M : 0 mg base/kg/day	
MEAN	1.053
SD	0.0260
N	4
Group: 2-M : 0.1 mg base/kg/day	
MEAN	1.042
SD	0.0292
N	4
Group: 3-M : 0.3 mg base/kg/day	
MEAN	1.073
SD	0.0121
N	4
Group: 4-M : 1.0 mg base/kg/day	
MEAN	1.060
SD	0.0223
N	4

LABCAT CC4.3

Table 8.4

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

SUMMARY OF URINALYSIS TESTS
TEST: Specific Gravity

STUDY ID: 134
STUDY NO: 134
ABBR: SG

SEX: FEMALE

UNITS: mg/mL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s): Week 5

Group: 1-F : 0 mg base/kg/day	
MEAN	1.064
SD	0.0133
N	4
Group: 2-F : 0.1 mg base/kg/day	
MEAN	1.056
SD	0.0297
N	4
Group: 3-F : 0.3 mg base/kg/day	
MEAN	1.061
SD	0.0262
N	4
Group: 4-F : 1.0 mg base/kg/day	
MEAN	1.062
SD	0.0496
N	4

LABCAT CC4.3

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 134
SEX: MALE

FATES: Scheduled Sacrifice DAYS: 28-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
Adrenal Glands (% BRAIN WEIGHT)				
MEAN	1.99	1.60	1.43	1.41
SD	0.529	0.036	0.295	0.080
N	4	4	4	4
Heart (% BRAIN WEIGHT)				
MEAN	107.19	114.31	101.01	97.92
SD	11.458	7.442	5.259	4.592
N	4	4	4	4
Kidneys (% BRAIN WEIGHT)				
MEAN	60.58	59.69	58.84	54.75
SD	8.754	5.763	7.095	7.316
N	4	4	4	4
Liver (% BRAIN WEIGHT)				
MEAN	330.57	341.00	346.49	360.88
SD	27.007	34.121	47.096	36.720
N	4	4	4	4
Spleen (% BRAIN WEIGHT)				
MEAN	41.06	39.25	46.32	73.06*
SD	9.702	7.159	10.722	9.846
N	4	4	4	4
Testes (% BRAIN WEIGHT)				
MEAN	18.46	15.95	15.47	15.95
SD	2.858	3.830	2.321	1.036
N	4	4	4	4
Thyroid+Parathyroids (% BRAIN WEIGHT)				
MEAN	1.18	1.06	1.61	0.98
SD	0.235	0.185	0.531	0.277
N	4	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-0.3 mg base/kg/day
(4)-1.0 mg base/kg/day
* - Significant difference $P < .05$

FOUR WEEK ORAL TOXICITY STUDY
OF WR242511 IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 134
SEX: FEMALE

FATES: Scheduled Sacrifice DAYS: 28-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
Adrenal Glands (% BRAIN WEIGHT)					
	MEAN	1.49	1.83	1.56	1.66
	SD	0.111	0.200	0.221	0.206
	N	4	4	4	4
Heart (% BRAIN WEIGHT)					
	MEAN	107.27	106.39	101.67	100.99
	SD	6.684	16.448	11.945	11.840
	N	4	4	4	4
Kidneys (% BRAIN WEIGHT)					
	MEAN	52.42	54.82	47.21	56.06
	SD	6.917	6.218	5.346	9.741
	N	4	4	4	4
Liver (% BRAIN WEIGHT)					
	MEAN	336.62	330.02	301.08	372.78
	SD	76.767	5.195	44.888	44.419
	N	4	4	4	4
Ovaries (% BRAIN WEIGHT)					
	MEAN	1.12	1.41	1.69	1.17
	SD	0.242	0.451	1.087	0.431
	N	4	4	4	4
Spleen (% BRAIN WEIGHT)					
	MEAN	37.72	40.74	46.04	96.86*
	SD	3.766	7.909	10.382	31.912
	N	4	4	4	4
Thyroid+Parathyroids (% BRAIN WEIGHT)					
	MEAN	1.08	1.16	1.03	1.15
	SD	0.230	0.121	0.131	0.153
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-0.3 mg base/kg/day
(8)-1.0 mg base/kg/day
* - Significant difference P < .05

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Table 10

FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS

Summary of Gross and Microscopic Lesions

GROSS LESIONS		Dose (mg base/kg/day)			
ORGAN - Lesion	Sex	0	0.1	0.3	1.0
LUNGS - White or yellow foci on apical lobe(s)	M	0/4	0/4	0/4	1/4
	F	0/4	0/4	0/4	2/4

MICROSCOPIC LESIONS[a,b]		Dose (mg base/kg/day)			
ORGAN - Lesion	Sex	0	0.1	0.3	1.0
LUNGS - Interstitial inflammation	M	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	3/4 (1.56)
	F	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	4/4 (1.50)
SPLEEN - Extramedullary hematopoiesis	M	0/4 (0.00)	1/4 (0.19)	0/4 (0.00)	4/4 (1.50)
	F	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	4/4 (1.50)
BONE MARROW - Hyperplasia	M	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	4/4 (0.75)
	F	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	4/4 (1.25)

[a]Incidence (mean group severity) - Determined by dividing the sum of all "weighted" severities for a finding by the number of tissues examined. The weighted averages are based upon the severity and distribution of the lesion.

[b]Lesion severity was scored as follows:

1 = Minimal 3 = Moderate
2 = Mild 4 = Marked

For additional information, see Pathology Report in Appendix 12.

Figure 1

FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS

SUMMARY OF MALE BODY WEIGHTS

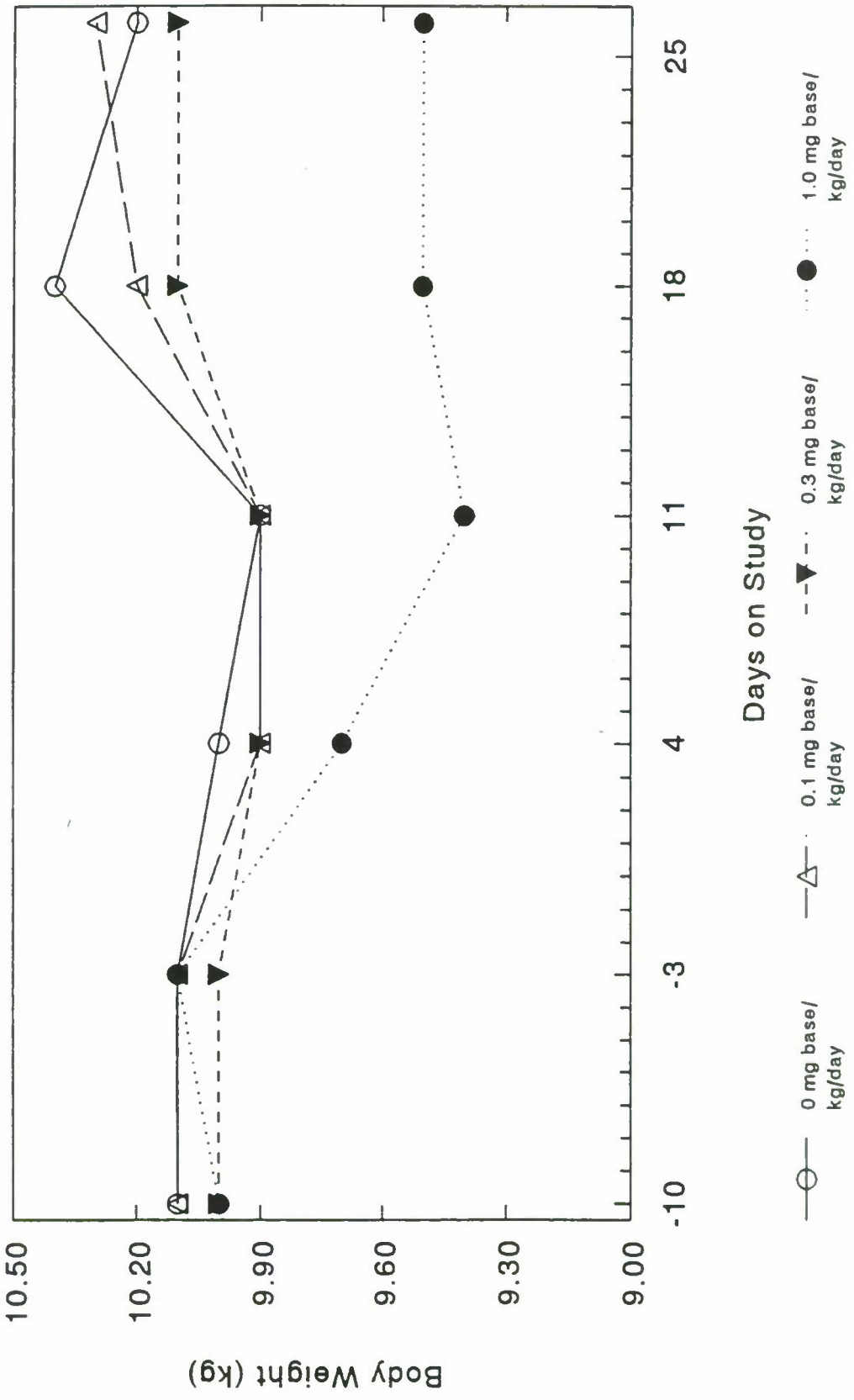
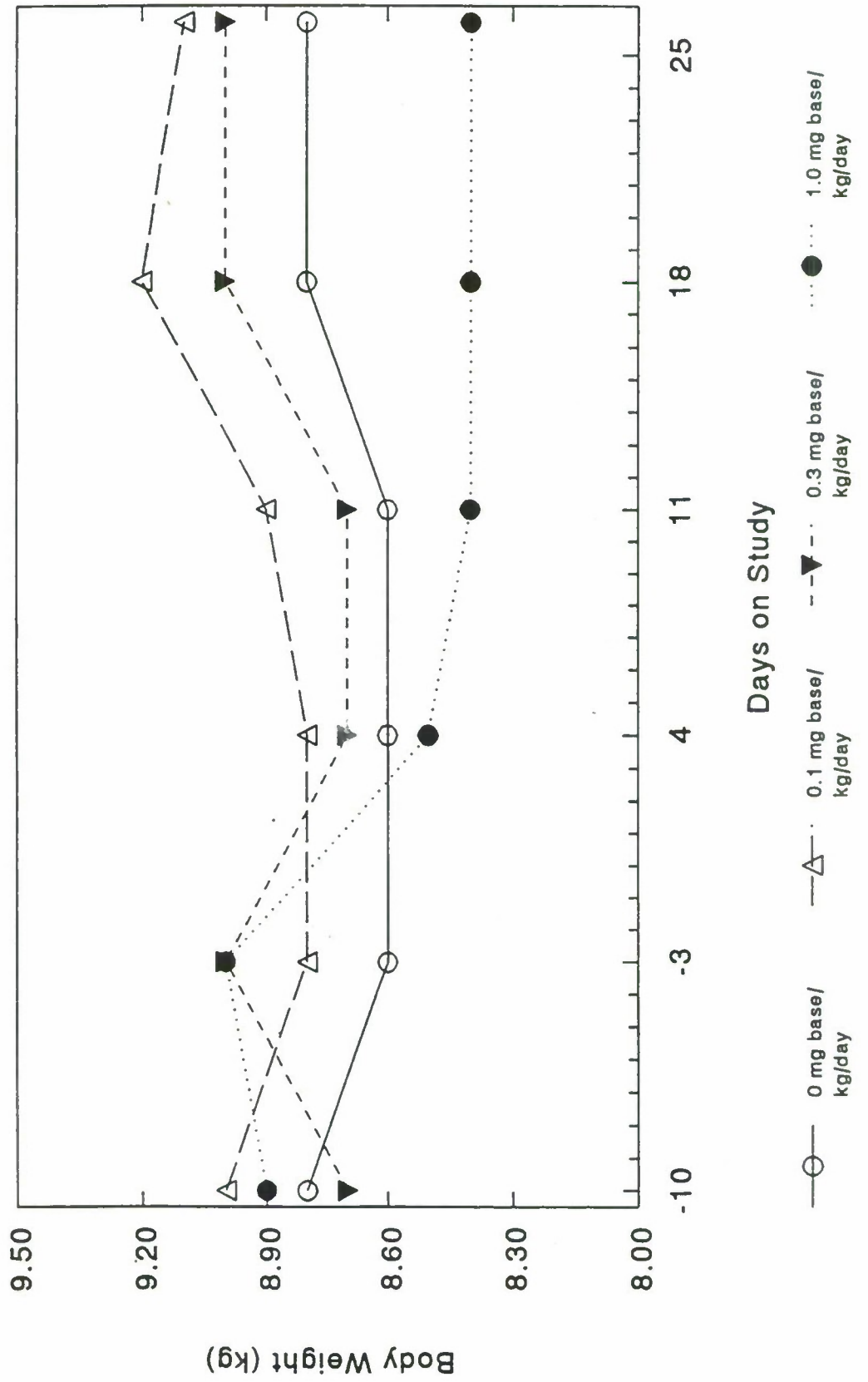


Figure 2

FOUR WEEK ORAL TOXICITY STUDY OF WR242511 IN DOGS

SUMMARY OF FEMALE BODY WEIGHTS



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APPENDIX 1

Analytical Chemistry Report

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FOUR WEEK ORAL TOXICITY STUDY OF 8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY-6-METHOXY-4-METHYLQUINOLINE DL-TARTRATE (WR242511) IN DOGS
STUDY NUMBER 134

Identity, Purity and Stability Study of WR242511

Analysts: Adam Negrusz
A. Karl Larsen, Jr.

Study Site: Drug Disposition Research Laboratory,
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

Sponsor: Toxicology Research Laboratory,
University of Illinois at Chicago
Chicago, Illinois 60612

Report Prepared by: Adam Negrusz, Ph.D.

Report Prepared: July 29, 1994

Approved: July 29, 1994
Dr. Eugene F. Woods, Ph.D.
Laboratory Director

Objective

The objective of this study was to confirm the identity, establish the purity and stability of WR242511.

Identification

GC-MS System

Gas Chromatograph:	Hewlett-Packard Series II
Mass Selective Detector:	Hewlett-Packard Model 5970
Analytical Column:	30 m x 0.25 mm ID, DB-5 with a 3 micron film thickness.
GC Parameters:	injector temp. 250°C, oven temp. 70°C initial, 280°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR242511 tartrate) was submitted from the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 0.71 μg base/ml and a 2 μl aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at rate of 1 scan per second.

Results - GC-MS

The mass spectrum indicates a molecular ion m/e 373 which is in agreement with the WR242511 free base molecular weight. Major fragments of WR242511 sample are m/e 84, 175, 203, 288.

Figure 1 shows the mass spectrum of the WR242511 sample.

Purity

Experimental

The subject sample (WR242511 tartrate) was supplied by the Toxicology Research Laboratory and stored at -20°C when it was not analyzed.

Description

A fine yellow powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure 2) recorded on a Shimadzu Spectronic 200 UV spectrometer (dual beam) was obtained from a 14.2 μg base/ml solution of WR242511 prepared in mobile phase. The sample was found with maximal absorptivity observed at 212 nm and 264 nm.

found with maximal absorptivity observed at 212 nm and 264 nm.

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 μl sample loop
Analytical Column:	Spherisorb CN 5 μ, 250 mm x 4.6 mm (Alltech)
Detector:	Perkin-Elmer LC-55B UV Detector, 225 nm, 264 nm
Integrator:	Spectra-Physics SP4270 Integrator
Mobile Phase:	20% methanol, 50% acetonitrile, 30% 0.01 M ammonium formate (in water), pH 3.0 (adjusted with 88% formic acid), flow 1.5 ml/minute

Procedure

Six solutions of WR242511 were prepared as follows. Twenty five mg of WR242511 sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 50 μl aliquot of each solution was immediately chromatographed at 225 nm and next at 264 nm.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR242511 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR242511 present in the sample:

$$\%\text{PURITY} = (\text{area of WR242511/total area}) \times 100$$

Results

Typical chromatograms are shown in Figure 3. The subject samples were found to contain less than 1% of one UV-absorbing impurity (225 nm). At 264 nm no visible impurities were observed. Percent purity of initial WR242511 sample was found to be 99.51%, standard deviation - 0.02%, terminal 99.50% $\pm$ 0.03%. The assay results are presented in Tables 1 and 2.

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FIGURE 1

MASS SPECTRUM OF WR242511 SAMPLE

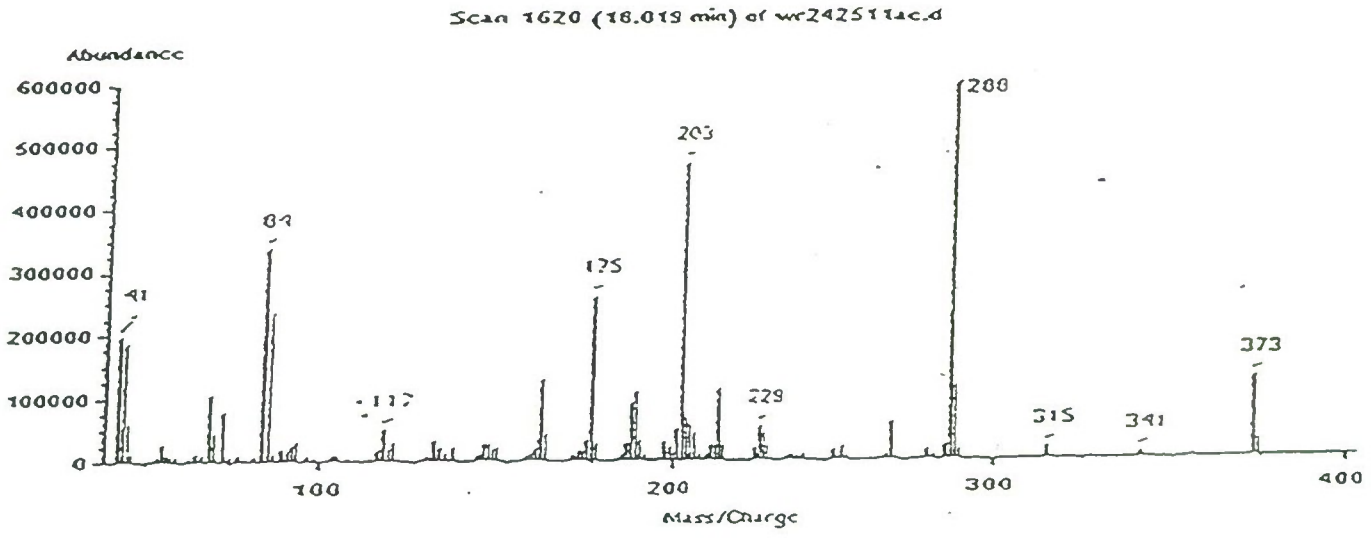

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FIGURE 2

ULTRAVIOLET SPECTRUM OF WR242511

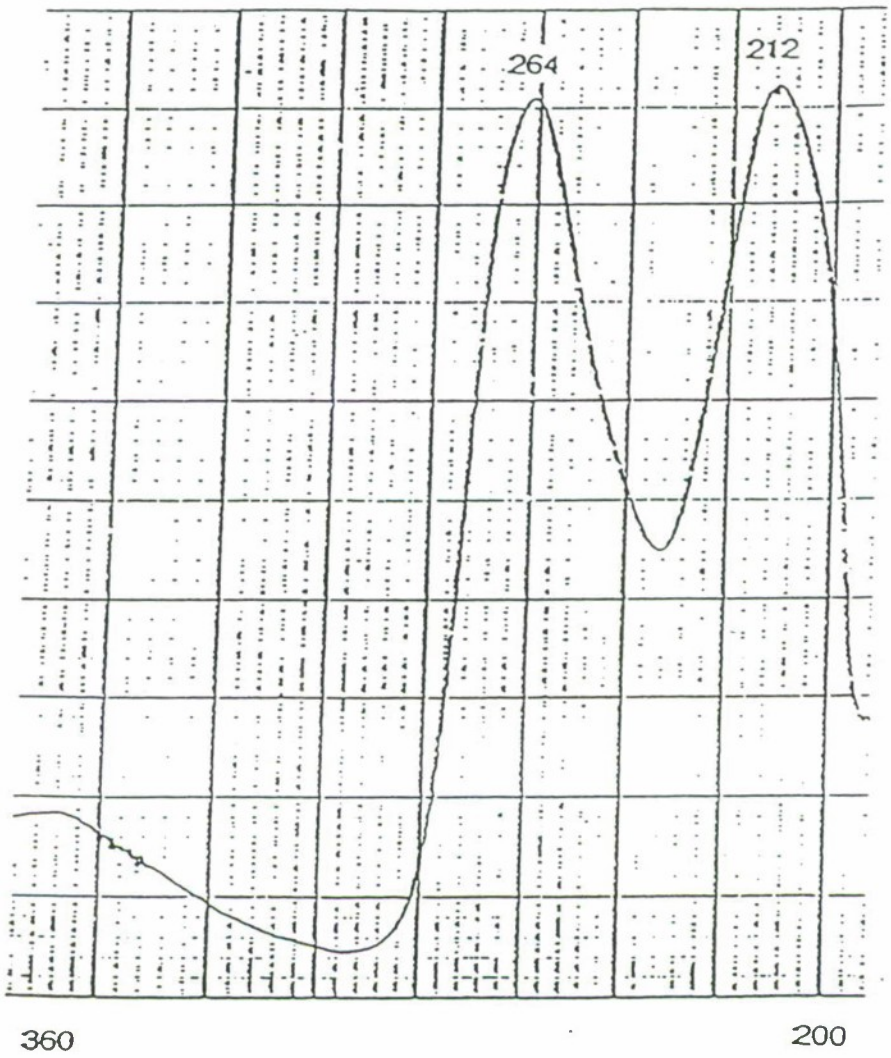
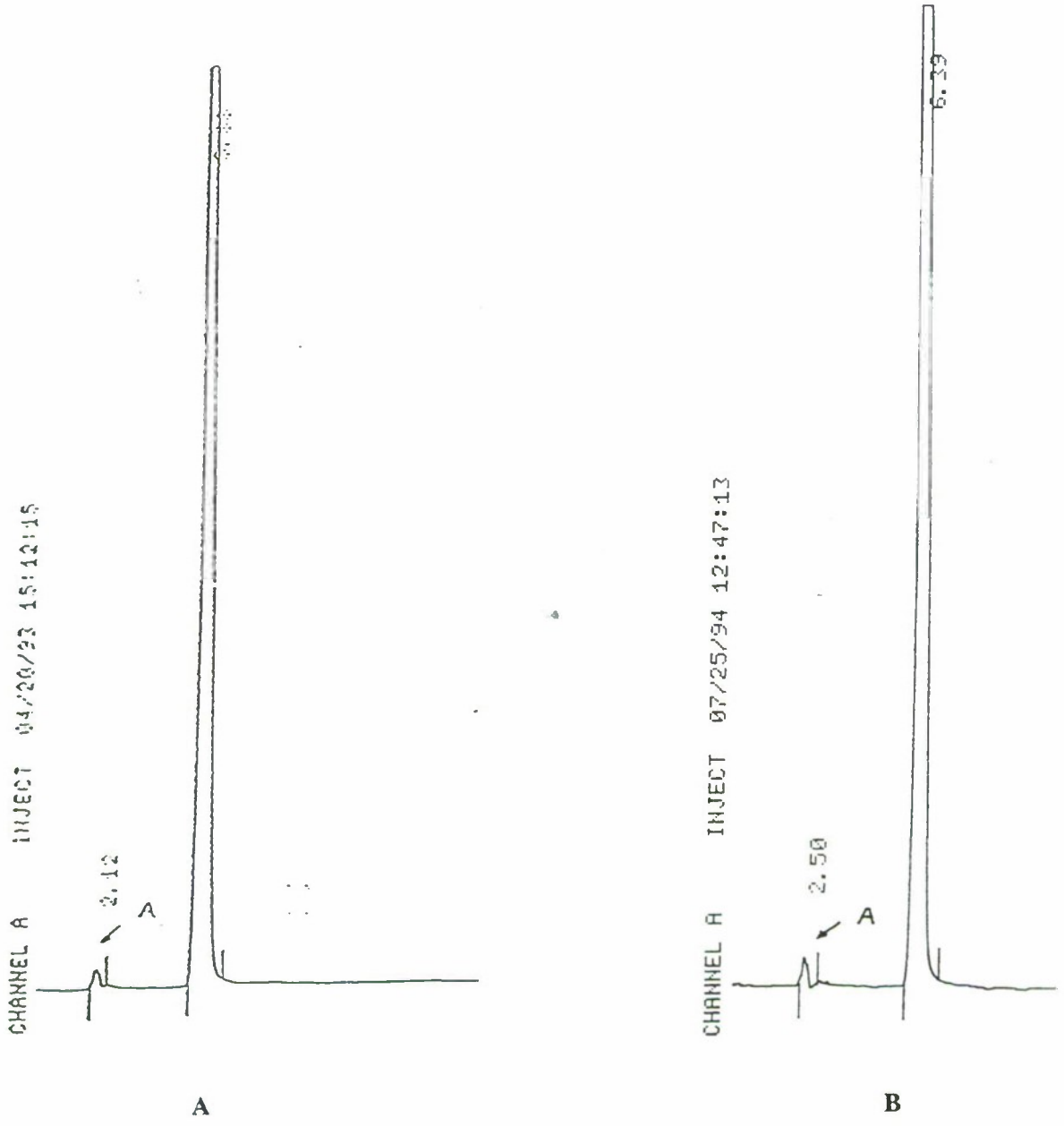


FIGURE 3

CHROMATOGRAMS OF WR242511 SAMPLE, CONC. 0.71 MG BASE/ML, 225 NM,
A - INITIAL SAMPLE, B - TERMINAL SAMPLE



A B

Table 1

Purity Data for WR242511
Initial Sample

Solutions

Peak Identity	1	2	3	2	5	6
A	4370	4354	4307	4414	3925	4509
WR242511	871097	863423	869317	869227	872867	862653
% Purity	99.501	99.498	99.507	99.495	99.552	99.480

Mean ± S.D. - 99.505 ± 0.024

Table 2

Purity Data for WR242511
Terminal Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	5074	4541	5512	4893	4604	4684
WR242511	986975	943444	978124	1001381	958985	940729
% Purity	99.489	99.521	99.440	99.514	99.522	99.505

Mean ± S.D. - 99.50 ± 0.03

APPENDIX 2

Clinical Pathology Methodology

Alanine Aminotransferase (ALT/GPT)

Modified Wroblewski & La Due procedure
Ciba-Corning 550 Express Clinical Chemistry System
Henry, R.J., Chiamori, N., Golub, O.J. and Berkman, S.
Am. J. Clin. Path., 34, 381, 1960.

Aspartate Aminotransferase (AST/GOT)

Modified Karmen procedure
Ciba-Corning 550 Express Clinical Chemistry System
Bergmeyer, H.V., Scheibe, P., and Wahlefeld, A.W.
Clin. Chem., 24, 58, 1978.

Total Protein

Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.R.
J. Biol. Chem. 131, 197, 1939.

Albumin

Bromocresol green method
Ciba-Corning 550 Express Clinical Chemistry System
Doumas, B.T. and Biggs, H.G.
Standard Methods of Clinical Chemistry, 7, 175, 1972.

Total Bilirubin

Modified Walters and Gerard method
Ciba-Corning 550 Express Clinical Chemistry System
Ertinghausen G., Fabiny-Byrd, D.L., Tiffany, T.O., and Carey, S.J.
Clinical Chem., 19, 1366, 1973.

Alkaline Phosphatase

Modified Bessey-Lowry procedure
Ciba-Corning 550 Express Clinical Chemistry System
Neumann, H. and Von Vreedendaal
M. Clin. Chem. Acta., 17, 183, 1967.

Gamma Glutamyl Transferase (GGT)

JFCC Methods for Gamms Glutamyl Transferase
Shaw, L.M., Stromme, J.H., London, J.L., Theodorsen, L.
J. Clin. Chem. C;in, Biochem. 21 (1983) 633-646

Cholesterol

Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Rosechlow, P., et. al
Z.F. Klin. Chem. V. Klin. Biochem. 12, 226, 1974.

Triglycerides

Tetrazolium salt reduction method
Ciba-Corning 550 Express Clinical Chemistry System
Klotzsch, S., et. al.
Advances Automated Analysis, Vol. 1, Mediad Inc., Tarrytown, N.Y., p. 111, 1973.

Lactate Dehydrogenase

L → P technique
Ciba-Corning 550 Express Clinical Chemistry System
Wacker, W.E.C., Ulmer, D.D., Valle, B.L.,
New England J Med. 225, 449, 1956

Creatine Kinase (CK)

Modification of Szasz *et al.* procedure
Ciba-Corning 550 Express Clinical Chemistry System
Clin. Chem. 22 650-656, 1976.

Urea Nitrogen (BUN)

Modified urease technique
Ciba-Corning 550 Express Clinical Chemistry System
Talke, H. and Schubert, G.E.
Klin. Wchnschr. 43, 174, 1965.

Creatinine

Jaffe method
Ciba-Corning 550 Express Clinical Chemistry System
Larsen. K.
Clin. Chem. Acta, 41, 209, 1972

Na+, K+

Ion specific electrodes
Model 614 ISE Na+/K+ Analyzer (Ciba Corning)

Chloride

Mecuric thiocyanate procedure
Ciba-Corning 550 Express Clinical Chemistry System
Zall, O.M., Fisher, D. and Garner, M.Q.
Anal. Chem, 28, 1065, 1956.

Calcium

Modified alizarin procedure
Ciba-Corning 550 Express Clinical Chemistry System
Frings, C.S., et. al.
Clin. Chem., 16, 816, 1970.

Phosphorus, Inorganic

Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Fiske, C.H. and Subbarow, Y.
J. Biol. Chem. 66, 325, 1925.

Glucose

Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Bondar, J.L. and Mead, D.C.
Clin. Chem. 20, 586, 1974.

Haptoglobin

Antigen-antibody method
Ciba-Corning 550 Express Clinical Chemistry System
Atlantic Antibodies Test Kit

Erythrocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Hemoglobin
Cyanomethemoglobin method
Sysmex K1000 Hematology Analyzer

Hematocrit
Indirect method; calculated value based on volume of red cells and volume of blood

Mean Corpuscular Volume (MCV)
Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)
Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)
Indirect method; calculated value based on hematocrit and hemoglobin

Reticulocyte Count
New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Heinz Bodies
Methyl Violet staining technique

Platelet Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Prothrombin Time (PT)
Electra 700 coagulation machine

Activated Partial Thromboplastin Time (APTT)
Electra 700 coagulation machine

Fibrinogen
Electra 700 coagulation machine

Leukocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Methemoglobin
Measured with a Co-oximeter (Instrumentation Laboratory Model 282)

Leukocyte Differential Count

- Neutrophils - Immature (bands)
- Neutrophils - Mature (segs)
- Monocytes
- Basophils
- Lymphocytes
- Eosinophils
- Wright stain procedure

  Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

Nucleated RBCs

- Wright stain procedure

  Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

RBC Morphology

- Wright stain procedure

  Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

URINALYSIS

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Qualitative Measurements

Ketones, Protein, Glucose, Blood, Bilirubin, Urobilinogen, Nitrite, Leukocytes, pH
Boehringer Mannheim Chemstrip 9 Reagent Strips

Specific Gravity

Optical temperature compensated refractometer

Microscopic Evaluation

Urinary sediment stained with kova-stain and evaluated using the Ames Atlas of Urine Sediment, Ames Co., Division Miles Laboratories, Elkhart, Indiana.

APPENDIX 3

Individual Observations (Clinical Signs)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 1-M SEX: MALE
DAY 0-DAY 29 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8172	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29
8143	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28
8148	Diarrhea	2		DAY 3
	Normal			DAY 0-DAY 2
	Normal			DAY 4-DAY 27
	Scheduled Sacrifice			DAY 28
8153	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28

Severity Codes

Observation	Severity No.	Description
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces
	3	Liquid feces

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 2-M SEX: MALE
DAY 0-DAY 29 DOSE: 0.1 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8173	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28
8170	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29
8147	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29
8151	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 3-M SEX: MALE
DAY 0-DAY 29 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8157	Blue Gums	1		DAY 28
	Blue Sclera	1		DAY 28
	Blue Tongue	1		DAY 12
	Blue Tongue	1		DAY 14-DAY 15
	Blue Tongue	1		DAY 28
	Diarrhea	2		DAY 7
	Normal			DAY 0-DAY 6
	Normal			DAY 8-DAY 11
	Normal			DAY 13
	Normal			DAY 16-DAY 27
	Scheduled Sacrifice			DAY 29
8159	Blue Sclera	1		DAY 7
	Blue Sclera	1		DAY 11-DAY 12
	Blue Sclera	1		DAY 14-DAY 24
	Blue Sclera	1		DAY 27
	Blue Tongue	1		DAY 4
	Blue Tongue	1		DAY 11-DAY 12
	Blue Tongue	1		DAY 14
	Blue Tongue	1		DAY 16-DAY 18
	Blue Tongue	1		DAY 27
	Normal			DAY 0-DAY 3
	Normal			DAY 5-DAY 6
	Normal			DAY 8-DAY 10
	Normal			DAY 13
	Normal			DAY 25-DAY 26
	Scheduled Sacrifice			DAY 28
8175	Blue Sclera	1		DAY 7
	Blue Sclera	1		DAY 18-DAY 21
	Blue Sclera	1		DAY 23-DAY 24
	Blue Sclera	1		DAY 27
	Blue Tongue	1		DAY 7
	Blue Tongue	1		DAY 15
	Blue Tongue	1		DAY 17
	Blue Tongue	1		DAY 25
	Normal			DAY 0-DAY 6

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 3-M SEX: MALE
DAY 0-DAY 29 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8175 (contd.)	Normal			DAY 8-DAY 14
	Normal			DAY 16
	Normal			DAY 22
	Normal			DAY 26
	Scheduled Sacrifice			DAY 28
8166	Blue Gums	1		DAY 15
	Blue Gums	1		DAY 25
	Blue Sclera	1		DAY 7
	Blue Sclera	1		DAY 15-DAY 17
	Blue Sclera	1		DAY 19-DAY 22
	Blue Tongue	1		DAY 15
	Blue Tongue	1		DAY 20
	Blue Tongue	1		DAY 23-DAY 25
	Blue Tongue	2		DAY 19
	Blue Tongue	2		DAY 21
	Normal			DAY 0-DAY 6
	Normal			DAY 8-DAY 14
	Normal			DAY 18
	Normal			DAY 26-DAY 27
	Scheduled Sacrifice			DAY 28

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-M SEX: MALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8146	Blue Gums	1		DAY 5-DAY 6
	Blue Gums	1		DAY 11-DAY 12
	Blue Gums	1		DAY 14-DAY 15
	Blue Gums	1		DAY 18-DAY 20
	Blue Gums	1		DAY 24
	Blue Gums	1		DAY 26-DAY 27
	Blue Gums	2		DAY 7
	Blue Gums	2		DAY 25
	Blue Sclera	1		DAY 5-DAY 27
	Blue Tongue	1		DAY 3-DAY 4
	Blue Tongue	1		DAY 6
	Blue Tongue	1		DAY 8-DAY 10
	Blue Tongue	1		DAY 13
	Blue Tongue	1		DAY 16
	Blue Tongue	1		DAY 21-DAY 24
	Blue Tongue	1		DAY 26-DAY 27
	Blue Tongue	2		DAY 5
	Blue Tongue	2		DAY 7
	Blue Tongue	2		DAY 11-DAY 12
	Blue Tongue	2		DAY 14-DAY 15
	Blue Tongue	2		DAY 17-DAY 20
	Blue Tongue	2		DAY 25
	Normal			DAY 0-DAY 2
	Scheduled Sacrifice			DAY 28
8156	Blue Gums	1		DAY 7
	Blue Gums	1		DAY 9-DAY 10
	Blue Gums	1		DAY 12-DAY 13
	Blue Gums	1		DAY 15
	Blue Gums	1		DAY 18-DAY 21
	Blue Gums	1		DAY 23-DAY 25
	Blue Sclera	1		DAY 5-DAY 25
	Blue Sclera	1		DAY 27-DAY 28
	Blue Tongue	1		DAY 5
	Blue Tongue	1		DAY 7-DAY 14
	Blue Tongue	1		DAY 16-DAY 24
	Blue Tongue	1		DAY 27-DAY 28

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-M SEX: MALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8156 (contd.)	Blue Tongue	2		DAY 15
	Blue Tongue	2		DAY 25
	Normal			DAY 0-DAY 4
	Normal			DAY 26
	Scheduled Sacrifice			DAY 29
8160	Blue Gums	1		DAY 3
	Blue Gums	1		DAY 6-DAY 14
	Blue Gums	1		DAY 16-DAY 21
	Blue Gums	1		DAY 23-DAY 25
	Blue Gums	1		DAY 27-DAY 28
	Blue Sclera	1		DAY 7-DAY 28
	Blue Tongue	1		DAY 3-DAY 10
	Blue Tongue	1		DAY 12-DAY 15
	Blue Tongue	1		DAY 18-DAY 28
	Blue Tongue	2		DAY 11
	Blue Tongue	2		DAY 16-DAY 17
	Normal			DAY 0-DAY 2
	Scheduled Sacrifice			DAY 29
8144	Blue Gums	1		DAY 3
	Blue Gums	1		DAY 5-DAY 6
	Blue Gums	1		DAY 8-DAY 10
	Blue Gums	1		DAY 12-DAY 20
	Blue Gums	1		DAY 26-DAY 27
	Blue Gums	2		DAY 7
	Blue Sclera	1		DAY 5-DAY 10
	Blue Sclera	1		DAY 12-DAY 27
	Blue Tongue	1		DAY 3-DAY 4
	Blue Tongue	1		DAY 13-DAY 15
	Blue Tongue	1		DAY 17
	Blue Tongue	1		DAY 21
	Blue Tongue	1		DAY 23-DAY 27
	Blue Tongue	2		DAY 5-DAY 10
	Blue Tongue	2		DAY 12
	Blue Tongue	2		DAY 16
	Blue Tongue	2		DAY 18-DAY 20
	Diarrhea	1		DAY 4

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-M SEX: MALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8144	Diarrhea	2		DAY 0
(contd.)	Normal			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 28
	Vomit Seen In Run			DAY 3

Severity Codes

Observation	Severity No.	Description
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces
	3	Liquid feces

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8211	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28
8214	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29
8184	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28
8180	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 0.1 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8207	Blue Tongue	1		DAY 8
	Normal			DAY 0-DAY 7
	Normal			DAY 9-DAY 27
	Scheduled Sacrifice			DAY 28
8206	Blue Sclera	1		DAY 22
	Normal			DAY 0-DAY 21
	Normal			DAY 23-DAY 28
	Scheduled Sacrifice			DAY 29
8185	Normal			DAY 0-DAY 27
	Scheduled Sacrifice			DAY 28
8199	Normal			DAY 0-DAY 28
	Scheduled Sacrifice			DAY 29

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8215	Blue Gums	1		DAY 7
	Blue Gums	1		DAY 18-DAY 20
	Blue Sclera	1		DAY 7
	Blue Sclera	1		DAY 14-DAY 15
	Blue Sclera	1		DAY 17-DAY 21
	Blue Sclera	1		DAY 23-DAY 25
	Blue Tongue	1		DAY 7-DAY 17
	Blue Tongue	1		DAY 20-DAY 21
	Blue Tongue	1		DAY 23-DAY 25
	Blue Tongue	1		DAY 27-DAY 28
	Blue Tongue	2		DAY 18-DAY 19
	Normal			DAY 0-DAY 6
	Normal			DAY 22
	Normal			DAY 26
	Scheduled Sacrifice			DAY 29
8193	Blue Sclera	1		DAY 12-DAY 16
	Blue Sclera	1		DAY 18-DAY 22
	Blue Sclera	1		DAY 27
	Blue Sclera	2		DAY 17
	Blue Tongue	1		DAY 4
	Blue Tongue	1		DAY 12
	Blue Tongue	1		DAY 14-DAY 16
	Blue Tongue	1		DAY 21-DAY 25
	Blue Tongue	2		DAY 17
	Normal			DAY 0-DAY 3
	Normal			DAY 5-DAY 11
	Normal			DAY 26
	Scheduled Sacrifice			DAY 28
8181	Blue Sclera	1		DAY 13
	Blue Sclera	1		DAY 15-DAY 17
	Blue Sclera	1		DAY 19-DAY 21
	Blue Sclera	1		DAY 28
	Blue Tongue	1		DAY 12-DAY 13
	Blue Tongue	1		DAY 16-DAY 18
	Blue Tongue	1		DAY 23-DAY 25

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8181	Blue Tongue	1		DAY 27-DAY 28
(contd.)	Blue Tongue	2		DAY 15
	Blue Tongue	2		DAY 19-DAY 21
	Normal			DAY 0-DAY 11
	Normal			DAY 14
	Normal			DAY 22
	Normal			DAY 26
	Scheduled Sacrifice			DAY 29
8197	Blue Gums	1		DAY 7
	Blue Gums	1		DAY 12
	Blue Gums	1		DAY 18-DAY 20
	Blue Sclera	1		DAY 7-DAY 8
	Blue Sclera	1		DAY 12
	Blue Sclera	1		DAY 14-DAY 24
	Blue Tongue	1		DAY 4
	Blue Tongue	1		DAY 6
	Blue Tongue	1		DAY 8-DAY 13
	Blue Tongue	1		DAY 15-DAY 16
	Blue Tongue	1		DAY 19
	Blue Tongue	1		DAY 21
	Blue Tongue	1		DAY 23-DAY 25
	Blue Tongue	2		DAY 7
	Blue Tongue	2		DAY 14
	Blue Tongue	2		DAY 17-DAY 18
	Blue Tongue	2		DAY 20
	Blue Tongue	2		DAY 27
	Normal			DAY 0-DAY 3
	Normal			DAY 5
	Normal			DAY 26
	Normal			DAY 28
	Scheduled Sacrifice			DAY 29
	Vomit Seen In Run			DAY 12

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8196	Blue Gums	1		DAY 7
	Blue Gums	1		DAY 12
	Blue Gums	1		DAY 15
	Blue Gums	1		DAY 20
	Blue Gums	1		DAY 25-DAY 26
	Blue Sclera	1		DAY 5-DAY 27
	Blue Tongue	1		DAY 5
	Blue Tongue	1		DAY 8-DAY 11
	Blue Tongue	1		DAY 13-DAY 14
	Blue Tongue	1		DAY 16
	Blue Tongue	1		DAY 18
	Blue Tongue	1		DAY 20
	Blue Tongue	1		DAY 22-DAY 24
	Blue Tongue	1		DAY 26-DAY 27
	Blue Tongue	2		DAY 7
	Blue Tongue	2		DAY 12
	Blue Tongue	2		DAY 15
	Blue Tongue	2		DAY 17
	Blue Tongue	2		DAY 19
	Blue Tongue	2		DAY 21
	Blue Tongue	2		DAY 25
	Normal			DAY 0-DAY 4
	Scheduled Sacrifice			DAY 28
8213	Blue Gums	1		DAY 13-DAY 16
	Blue Gums	1		DAY 23-DAY 27
	Blue Gums	2		DAY 3
	Blue Gums	2		DAY 5-DAY 10
	Blue Gums	2		DAY 12
	Blue Gums	2		DAY 17-DAY 20
	Blue Sclera	1		DAY 6-DAY 10
	Blue Sclera	1		DAY 12-DAY 27
	Blue Tongue	1		DAY 4
	Blue Tongue	1		DAY 13
	Blue Tongue	1		DAY 15
	Blue Tongue	1		DAY 21-DAY 22
	Blue Tongue	1		DAY 26

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8213	Blue Tongue	2		DAY 3
(contd.)	Blue Tongue	2		DAY 5-DAY 10
	Blue Tongue	2		DAY 12
	Blue Tongue	2		DAY 14
	Blue Tongue	2		DAY 16-DAY 20
	Blue Tongue	2		DAY 23-DAY 25
	Blue Tongue	2		DAY 27
	Normal			DAY 0-DAY 2
	Scheduled Sacrifice			DAY 28
8194	Blue Gums	1		DAY 5-DAY 10
	Blue Gums	1		DAY 12-DAY 13
	Blue Gums	1		DAY 15-DAY 16
	Blue Gums	1		DAY 18-DAY 28
	Blue Gums	2		DAY 11
	Blue Gums	2		DAY 14
	Blue Gums	2		DAY 17
	Blue Sclera	1		DAY 4-DAY 5
	Blue Sclera	1		DAY 7
	Blue Sclera	1		DAY 11-DAY 25
	Blue Sclera	1		DAY 27-DAY 28
	Blue Tongue	1		DAY 6-DAY 10
	Blue Tongue	1		DAY 12-DAY 13
	Blue Tongue	1		DAY 19-DAY 20
	Blue Tongue	1		DAY 24-DAY 25
	Blue Tongue	2		DAY 4-DAY 5
	Blue Tongue	2		DAY 11
	Blue Tongue	2		DAY 14-DAY 18
	Blue Tongue	2		DAY 21-DAY 23
	Blue Tongue	2		DAY 26-DAY 28
	Normal			DAY 0-DAY 3
	Scheduled Sacrifice			DAY 29
8182	Blue Gums	1		DAY 3
	Blue Gums	1		DAY 6
	Blue Gums	1		DAY 8-DAY 14
	Blue Gums	1		DAY 16-DAY 20
	Blue Gums	1		DAY 24-DAY 26

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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INDIVIDUAL CLINICAL SIGNS

STUDY: 134 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 29 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8182 (contd.)	Blue Gums	1		DAY 28
	Blue Gums	2		DAY 7
	Blue Sclera	1		DAY 4
	Blue Sclera	1		DAY 6
	Blue Sclera	1		DAY 8-DAY 21
	Blue Sclera	1		DAY 25-DAY 28
	Blue Sclera	2		DAY 7
	Blue Sclera	2		DAY 22-DAY 24
	Blue Tongue	1		DAY 5
	Blue Tongue	1		DAY 8
	Blue Tongue	1		DAY 13
	Blue Tongue	1		DAY 15
	Blue Tongue	1		DAY 18-DAY 27
	Blue Tongue	2		DAY 3-DAY 4
	Blue Tongue	2		DAY 6-DAY 7
	Blue Tongue	2		DAY 9-DAY 12
	Blue Tongue	2		DAY 14
	Blue Tongue	2		DAY 16-DAY 17
	Blue Tongue	2		DAY 28
	Normal			DAY 0-DAY 2
	Scheduled Sacrifice			DAY 29

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
DAY 0					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
2		0	0	0	1 25%
DAY 1					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 2					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 3					
No. Observed		4	4	4	4
Normal		3 75%	4 100%	4 100%	1 25%
Blue Gums					
SEV					
1		0	0	0	2 50%
Blue Tongue					
SEV					
1		0	0	0	3 75%
Diarrhea					
SEV					
2		1 25%	0	0	0
Vomit Seen In Run		0	0	0	1 25%
DAY 4					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	1 25%
Blue Tongue					
SEV					
1		0	0	1 25%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 5					

Severity Codes

Observation	Severity No.	Description
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces
	3	Liquid feces

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 5	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	2 50%
	DAY 6				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	DAY 7				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	0	2 50%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 7	Diarrhea				
	SEV				
	2	0	0	1 25%	0
	DAY 8				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	0	4 100%
	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	2	0	0	0	1 25%
	DAY 9				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	0	4 100%
	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	2	0	0	0	1 25%
	DAY 10				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	0	4 100%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 10	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	2	0	0	0	1 25%
	DAY 11				
	No. Observed	4	4	4	3
	Normal	4 100%	4 100%	3 75%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 67%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	3 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	1 33%
	2	0	0	0	2 67%
	DAY 12				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	2 50%
	DAY 13				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 13	1	0	0	0	4 100%
	Blue Tongue				
	SEV				
	1	0	0	0	4 100%
	DAY 14				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	3 75%
	2	0	0	0	1 25%
	DAY 15				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	1 25%	3 75%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	3 75%	2 50%
	2	0	0	0	2 50%
	DAY 16				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 16	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	0	2 50%
	DAY 17				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	2 50%
	DAY 18				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	0	2 50%
	DAY 19				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 19	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
	2	0	0	1 25%	2 50%
	DAY 20				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	0	2 50%
	DAY 21				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	0	4 100%
	2	0	0	1 25%	0
	DAY 22				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 22	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	DAY 23				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	4 100%
	DAY 24				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	4 100%
	DAY 25				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	0	4 100%
	Blue Tongue				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 25	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	2 50%
	DAY 26				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	1 25%
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	DAY 27				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	4 100%
	DAY 28				
	No. Observed	4	4	4	4
	Scheduled Sacrifice	3 75%	1 25%	3 75%	2 50%
	Normal	1 25%	3 75%	0	0
	Blue Gums				
	SEV				
	1	0	0	1 25%	1 25%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	2 50%
	Blue Tongue				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	0.3 3-M	1.0 (mg base/kg/day) 4-M
Day 28	SEV 1	0	0	1 25%	2 50%
	DAY 29				
	No. Observed	1	3	1	2
	Scheduled Sacrifice	1 100%	3 100%	1 100%	2 100%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
DAY 0					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 1					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 2					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 3					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Gums					
SEV					
1		0	0	0	1 25%
2		0	0	0	1 25%
Blue Tongue					
SEV					
2		0	0	0	2 50%
DAY 4					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	2 50%	1 25%
Blue Sclera					
SEV					
1		0	0	0	2 50%
Blue Tongue					
SEV					
1		0	0	2 50%	1 25%
2		0	0	0	2 50%
DAY 5					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	0
Blue Gums					
SEV					
1		0	0	0	1 25%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 5	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	0	2 50%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	2 50%
	DAY 6				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	1 25%
	2	0	0	0	2 50%
	DAY 7				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	2 50%	3 75%
	2	0	0	0	1 25%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	1 25%
	2	0	0	1 25%	3 75%
	DAY 8				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 8	No. Observed	4	4	4	4
	Normal	4 100%	3 75%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	3 75%
	Blue Tongue				
	SEV				
	1	0	1 25%	2 50%	3 75%
	2	0	0	0	1 25%
	DAY 9				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	2 50%
	DAY 10				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	2 50%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

	PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 10	1		0	0	2 50%	2 50%
	2		0	0	0	2 50%
	DAY 11					
	No. Observed		4	4	4	3
	Normal		4 100%	4 100%	2 50%	0
	Blue Gums					
	SEV					
	1		0	0	0	1 33%
	2		0	0	0	1 33%
	Blue Sclera					.
	SEV					
	1		0	0	0	3 100%
	Blue Tongue					
	SEV					
	1		0	0	2 50%	1 33%
	2		0	0	0	2 67%
	DAY 12					
	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	0	0
	Blue Gums					
	SEV					
	1		0	0	1 25%	3 75%
	2		0	0	0	1 25%
	Blue Sclera					
	SEV					
	1		0	0	2 50%	4 100%
	Blue Tongue					
	SEV					
	1		0	0	4 100%	1 25%
	2		0	0	0	3 75%
	Vomit Seen In Run		0	0	1 25%	0
	DAY 13					
	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	0	0
	Blue Gums					
	SEV					
	1		0	0	0	3 75%
	Blue Sclera					

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 13	SEV				
	1	0	0	2 50%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	3 75%	4 100%
	DAY 14				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	1 25%
	2	0	0	1 25%	3 75%
	DAY 15				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%
	Blue Sclera				
	SEV				
	1	0	0	4 100%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	3 75%	2 50%
	2	0	0	1 25%	2 50%
	DAY 16				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	3 75%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 16	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	4 100%	1 25%
	2	0	0	0	3 75%
	DAY 17				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	1 25%
	2	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	2	0	0	1 25%	0
	Blue Tongue				
	SEV				
	1	0	0	2 50%	0
	2	0	0	2 50%	4 100%
	DAY 18				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	3 75%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	2 50%	2 50%
	DAY 19				
	No. Observed	4	4	4	4

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 19	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	4 100%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	2 50%
	2	0	0	2 50%	2 50%
	DAY 20				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	2 50%	3 75%
	2	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	4 100%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	3 75%
	2	0	0	2 50%	1 25%
	DAY 21				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	1 25%
	Blue Sclera				
	SEV				
	1	0	0	4 100%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	3 75%	2 50%
	2	0	0	1 25%	2 50%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
DAY 22					
No. Observed		4	4	4	4
Normal		4 100%	3 75%	2 50%	0
Blue Gums					
SEV					
1		0	0	0	1 25%
Blue Sclera					
SEV					
1		0	1 25%	2 50%	3 75%
2		0	0	0	1 25%
Blue Tongue					
SEV					
1		0	0	1 25%	3 75%
2		0	0	0	1 25%
DAY 23					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	0	0
Blue Gums					
SEV					
1		0	0	0	2 50%
Blue Sclera					
SEV					
1		0	0	2 50%	3 75%
2		0	0	0	1 25%
Blue Tongue					
SEV					
1		0	0	4 100%	2 50%
2		0	0	0	2 50%
DAY 24					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	0	0
Blue Gums					
SEV					
1		0	0	0	3 75%
Blue Sclera					
SEV					
1		0	0	2 50%	3 75%
2		0	0	0	1 25%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 24	Blue Tongue				
	SEV				
	1	0	0	4 100%	3 75%
	2	0	0	0	1 25%
	DAY 25				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	4 100%	2 50%
	2	0	0	0	2 50%
	DAY 26				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	0
	Blue Gums				
	SEV				
	1	0	0	0	4 100%
	Blue Sclera				
	SEV				
	1	0	0	0	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	3 75%
	2	0	0	0	1 25%
	DAY 27				
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	0	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 134 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	0.3 3-F	1.0 (mg base/kg/day) 4-F
Day 27	1	0	0	1 25%	4 100%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	2 50%
	2	0	0	1 25%	2 50%
	DAY 28				
	No. Observed	4	4	4	4
	Scheduled Sacrifice	2 50%	2 50%	1 25%	2 50%
	Normal	2 50%	2 50%	1 25%	0
	Blue Gums				
	SEV				
	1	0	0	0	2 50%
	Blue Sclera				
	SEV				
	1	0	0	1 25%	2 50%
	Blue Tongue				
	SEV				
	1	0	0	2 50%	0
	2	0	0	0	2 50%
	DAY 29				
	No. Observed	2	2	3	2
	Scheduled Sacrifice	2 100%	2 100%	3 100%	2 100%

Severity Codes

Observations	Severity No.	Description
Blue Gums/ Blue Tongue/ Blue Sclera	1	Mild (easily seen, blue color)
	2	Marked (deep blue-purple color)

APPENDIX 4

Individual Body Weights and Body Weight Gains

FOUR WEEK ORAL TOXICITY STUDY
OF WR24511 IN DOGS

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8172	10.5	10.3	10.0	9.7	10.0	10.0
8143	10.1	10.2	10.3	10.4	10.9	10.6
8148	9.9	10.0	9.9	9.9	10.4	10.1
8153	9.8	10.0	9.7	9.7	10.1	10.2
MEAN	10.1	10.1	10.0	9.9	10.4	10.2
S.D.	0.31	0.15	0.25	0.33	0.40	0.26
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8173	10.9	10.9	10.8	11.0	11.3	11.5
8170	10.4	10.3	10.3	10.2	10.6	10.7
8147	10.0	9.9	9.6	9.6	9.8	9.9
8151	9.2	9.1	9.0	8.9	9.1	9.2
MEAN	10.1	10.1	9.9	9.9	10.2	10.3
S.D.	0.72	0.76	0.79	0.89	0.96	0.99
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 3-M SEX: MALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8157	10.9	10.8	10.5	10.5	10.7	10.8
8159	9.5	9.5	9.5	9.4	9.9	9.8
8175	9.6	9.8	9.6	9.3	9.3	9.2
8166	10.0	10.0	10.0	10.2	10.4	10.7
MEAN	10.0	10.0	9.9	9.9	10.1	10.1
S.D.	0.64	0.56	0.45	0.59	0.61	0.76
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 4-M SEX: MALE
DOSE: 1.0 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8146	10.6	10.3	10.2	9.6	9.5	9.2
8156	10.2	9.8	9.7	9.4	9.7	9.8
8160	10.2	10.0	10.1	10.1	10.1	10.3
8144	9.0	10.3	8.6	8.3	8.5	8.6
MEAN	10.0	10.1	9.7	9.4	9.5	9.5
S.D.	0.69	0.24	0.73	0.76	0.68	0.74
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8211	9.3	9.3	9.4	9.4	10.1	10.0
8214	9.0	8.9	8.9	8.9	8.8	8.8
8184	8.6	8.2	8.0	7.9	8.3	8.4
8180	8.4	8.1	8.1	8.1	8.1	8.0
MEAN	8.8	8.6	8.6	8.6	8.8	8.8
S.D.	0.40	0.57	0.67	0.70	0.90	0.86
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8207	9.2	8.7	8.8	8.7	8.8	8.7
8206	9.0	8.9	8.8	8.8	9.2	9.2
8185	8.5	8.3	8.4	8.6	9.2	8.9
8199	9.1	9.1	9.3	9.4	9.7	9.7
MEAN	9.0	8.8	8.8	8.9	9.2	9.1
S.D.	0.31	0.34	0.37	0.36	0.37	0.43
N	4	4	4	4	4	4

--: Data Unavailable

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 3-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8215	9.2	9.2	9.6	9.5	9.8	9.8
8193	9.0	8.9	8.9	9.0	9.1	9.3
8181	8.5	8.4	8.4	8.4	8.9	8.8
8197	8.2	9.4	8.0	7.9	8.2	8.2
MEAN	8.7	9.0	8.7	8.7	9.0	9.0
S.D.	0.46	0.43	0.69	0.70	0.66	0.68
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 134 GROUP: 4-F SEX: FEMALE
DOSE: 1.0 (mg base/kg/day)

ANIMAL #	DAY -10	DAY -3	DAY 4	DAY 11	DAY 18	DAY 26
8196	9.8	9.5	9.2	9.2	9.4	9.2
8213	8.8	9.9	8.4	8.1	8.0	8.0
8194	8.7	8.7	8.7	8.5	8.6	8.8
8182	8.2	7.9	7.7	7.6	7.6	7.7
MEAN	8.9	9.0	8.5	8.4	8.4	8.4
S.D.	0.67	0.89	0.63	0.68	0.78	0.69
N	4	4	4	4	4	4

--: Data Unavailable

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INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8172	-0.3	-0.3	0.3	0.0	-0.3
8143	0.1	0.1	0.5	-0.3	0.4
8148	-0.1	0.0	0.5	-0.3	0.1
8153	-0.3	0.0	0.4	0.1	0.2
MEAN	-0.2	-0.1	0.4	-0.1	0.1
S.D.	0.19	0.17	0.10	0.21	0.29
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8173	-0.1	0.2	0.3	0.2	0.6
8170	0.0	-0.1	0.4	0.1	0.4
8147	-0.3	0.0	0.2	0.1	0.0
8151	-0.1	-0.1	0.2	0.1	0.1
MEAN	-0.1	0.0	0.3	0.1	0.3
S.D.	0.13	0.14	0.10	0.05	0.28
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 3-M SEX: MALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8157	-0.3	0.0	0.2	0.1	0.0
8159	0.0	-0.1	0.5	-0.1	0.3
8175	-0.2	-0.3	0.0	-0.1	-0.6
8166	0.0	0.2	0.2	0.3	0.7
MEAN	-0.1	-0.1	0.2	0.1	0.1
S.D.	0.15	0.21	0.21	0.19	0.55
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

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INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 4-M SEX: MALE
DOSE: 1.0 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8146	-0.1	-0.6	-0.1	-0.3	-1.1
8156	-0.1	-0.3	0.3	0.1	0.0
8160	0.1	0.0	0.0	0.2	0.3
8144	-1.7	-0.3	0.2	0.1	-1.7
MEAN	-0.5	-0.3	0.1	0.0	-0.6
S.D.	0.84	0.24	0.18	0.22	0.94
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

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INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8211	0.1	0.0	0.7	-0.1	0.7
8214	0.0	0.0	-0.1	0.0	-0.1
8184	-0.2	-0.1	0.4	0.1	0.2
8180	0.0	0.0	0.0	-0.1	-0.1
MEAN	0.0	0.0	0.3	0.0	0.2
S.D.	0.13	0.05	0.37	0.10	0.38
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

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INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8207	0.1	-0.1	0.1	-0.1	0.0
8206	-0.1	0.0	0.4	0.0	0.3
8185	0.1	0.2	0.6	-0.3	0.6
8199	0.2	0.1	0.3	0.0	0.6
MEAN	0.1	0.1	0.4	-0.1	0.4
S.D.	0.13	0.13	0.21	0.14	0.29
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

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INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 3-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8215	0.4	-0.1	0.3	0.0	0.6
8193	0.0	0.1	0.1	0.2	0.4
8181	0.0	0.0	0.5	-0.1	0.4
8197	-1.4	-0.1	0.3	0.0	-1.2
MEAN	-0.3	0.0	0.3	0.0	0.1
S.D.	0.79	0.10	0.16	0.13	0.84
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 134 GROUP: 4-F SEX: FEMALE
DOSE: 1.0 (mg base/kg/day)

ANIMAL #	DAY 4[b]	DAY 11	DAY 18	DAY 26	TOTAL GAIN
8196	-0.3	0.0	0.2	-0.2	-0.3
8213	-1.5	-0.3	-0.1	0.0	-1.9
8194	0.0	-0.2	0.1	0.2	0.1
8182	-0.2	-0.1	0.0	0.1	-0.2
MEAN	-0.5	-0.2	0.1	0.0	-0.6
S.D.	0.68	0.13	0.13	0.17	0.90
N	4	4	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day -3